The Developmental, Diagnostic and Dimensional Interview - Short Form Adult Version (3Di-sva): a tool for assessing autism spectrum disorders in adults – validation in a clinical population

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D.Clin.Psy. thesis (Volume 1), 2016

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Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Overview

This thesis focuses on the assessment of autism spectrum disorder (ASD) in individuals who have reached adulthood without ever having received a diagnosis and, in particular, on distinguishing features of ASD from those of other mental health difficulties in a potentially complex adult clinical population.

Part 1: This section systematically reviews literature estimating levels of co-occurrence of ASD and psychotic disorders. Fourteen studies investigating the prevalence of psychosis in adults diagnosed with ASD and six studies estimating the prevalence of ASD in adults diagnosed with a psychotic disorder were included. The review concludes that lifetime prevalence of psychosis in adults with ASD may be higher than in the general population and explores factors which might explain an association between these disorders.

Part 2: This section is an empirical paper reporting a study designed to validate the Developmental, Diagnostic and Dimensional Interview - Short Form Adult Version (3Di-sva) in a clinical population. The 3Di-sva is a new informant-report interview for the diagnosis of ASD in adults. The interview was conducted in respect of 27 individuals diagnosed with ASD and 20 clinical comparison participants diagnosed with a range of mental health difficulties. The 3Di-sva was found to display good psychometric properties including interrater reliability, internal consistency, criterion validity and sensitivity and specificity. This research was conducted in collaboration with another UCL Clinical Psychology Doctorate student (Clarke, 2015) who evaluated the psychometric properties of the 3Di-sva when used in a non-clinical comparison population.

Part 3: This section provides a critical appraisal of the systematic literature review and major research project, reflecting on aspects of clinical experience which

contributed to the work undertaken, ways in which the process of carrying out the study influenced my perspective on research and clinical practice, and methodological challenges that were encountered.

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Acknowledgements

I would like to thank all the individuals who have given up their time to take part in this study.

I am extremely grateful to Dr Will Mandy for his supervision, advice, unceasing encouragement - and use of inspirational sporting metaphors - throughout this long process. I would like to thank Kiri Clarke for being the best research collaborator anyone could wish for. I cannot begin to list the ways in which she has helped me, quite simply, I would not have got to the end without her.

Huge thanks to Dr Claire Williams for her invaluable support, ideas and unfailing sense of humour. Thanks also to all the clinicians across North East London Foundation Trust who welcomed me into their services and helped me with recruitment. Thanks to Dr Jason Crabtree, who continued to provide support throughout this project, as well as to Dr Andre Strydom, Dr Andrew Greenhill and all the other clinicians at the ASD clinics where we recruited. Thanks to Robert Cobb who stepped up to provide emergency interrater reliability scoring.

I am grateful to my UCL colleagues for supporting me throughout this process, in particular, Anneka Holden, Alyssa Joye and Jessica Karalus. Finally, to my parents, to Miriam Shea, and to all my other friends, who have patiently weathered the many months of exhaustion, back spasm and cave-like existence – thank you!

PART 1: LITERATURE REVIEW

Co-occurrence of autism spectrum disorders and psychosis

Abstract

Background. Autism spectrum disorder (ASD) and psychotic disorders share a complex, related history underpinned by a longstanding interest in the possibility of an association between them, recognising commonalities in areas of behavioural phenotype, susceptibility genes and sociocognitive functioning. Nevertheless, the relationship between ASD and psychosis remains unclear and evidence as to whether each of: (i) prevalence of psychosis in adults with ASD, and (ii) prevalence of ASD in adults with psychosis, may be higher than in the general population is equivocal.

Aim. To review current literature investigating the prevalence of psychosis among adults diagnosed with ASD and the prevalence of ASD among adults diagnosed with a psychotic disorder.

Method. Systematic literature searches were performed using Psychinfo and OVID MEDLINE and manual searches of reference lists. These searches identified 20 articles meeting quality and relevance criteria for review.

Results. There is conflicting evidence regarding the co-occurrence of ASD and psychosis, with prevalence estimates varying widely and studies investigating the issue tending to be associated with a certain risk of bias. Prevalence estimates of psychosis in adults with ASD, as reported in the included studies, ranged widely from 0% to 61.5%. However, based on the results of this review, it is suggested that the lifetime prevalence of psychosis in adults with ASD may be higher than in the general population at around 12-13%. Estimates of prevalence of ASD in adults with psychotic disorders ranged from 0.8% to 27% in the studies reviewed. These studies were too few in number, associated with too great a risk of bias and too heterogenous for a meaningful conclusion to be reached as to the likely prevalence of ASD in a psychosis population.

Conclusions. Clinicians working in adult ASD and psychosis services need to be mindful of the possibility of co-occurrence when assessing individuals. Additional, well-designed, population based studies are needed to determine the true level of co-occurrence of these disorders.

Introduction

Autism spectrum disorder (ASD) is a lifelong developmental condition characterised by two groups of symptoms: (i) social communication and interaction difficulties, and (ii) restricted, repetitive behaviours and unusual sensory perception (Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; *DSM-5*; American Psychiatric Association [APA], 2013a). There is evidence that many individuals with ASD will experience other mental health difficulties during their lives, (Geurts & Jansen, 2011; Mukaddes, Hergüner, & Tanidir, 2010). Given the impact that such comorbidity may have on the long term outcome, quality of life and functioning of these individuals, it is important that coexisting conditions are recognised (National Institute for Health and Clinical Excellence [NICE], 2011).

One such group of potentially coexisting mental health conditions is the psychotic disorders, characterised by a significant alteration of an individual's thoughts, mood, behaviour and perception (NICE, 2014). DSM-5 (APA, 2013a) describes "schizophrenia spectrum and other psychotic disorders" as being characterised by dysfunction in one or more of five domains: delusions (beliefs that are rigidly held notwithstanding conflicting evidence), hallucinations (perceiving something in the absence of an external stimulus), disorganised thought (manifesting in disorganised speech), grossly disorganised or abnormal motor behaviour and negative symptoms (such as, diminished emotional expression and low motivation). Psychotic disorders are recognised as being heterogeneous, with considerable variation in the combination of symptoms experienced by individuals and in the course which these disorders may follow (NICE, 2014).

Autism and psychosis share a complex, intertwined history. In 1911 Eugen Bleuler used the term 'autism' to describe a key feature he observed in

schizophrenia, that is, a withdrawal by the individual from outer reality in favour of a retreat into the inner world (Parnas, 2011). In 1943 Leo Kanner borrowed the term 'autistic' from the schizophrenia literature to describe a group of children he observed in the clinic displaying 'extreme aloneness' and a strong, obsessive wish to preserve sameness (Kanner, 1943). This was the first published account of autism as a distinct syndrome characterised by traits which are now typically associated with the modern conceptualisation of ASD. Throughout the 1950s and 1960s, autism was widely regarded as a psychotic disorder (DSM-II; APA, 1968) and the term was often used interchangeably with 'childhood schizophrenia'. By the 1970s, Michael Rutter's research was contributing to the reconceptualisation of autism as a neurodevelopmental disorder that was qualitatively distinct from psychosis (Rutter, 1978). Rutter (1978) set out a number of key criteria according to which the syndrome of autism might be identified: (i) onset prior to 30 months of age, (ii) impaired social development, (iii) delayed and unusual language development and (iv) 'insistence on sameness' or stereotyped behaviours and routines, and he established the validity of this syndrome as one distinct from other clinical disorders. Consequentially, in 1980 the Diagnostic and the Statistical Manual of Mental Disorders, Third Edition (*DSM-III*; APA) defined infantile autism as a pervasive developmental disorder distinct from schizophrenia.

Recently there has been a revived interest in the possibility of an association between ASD and psychosis, recognising overlap in areas of behavioural phenotype, susceptibility genes and sociocognitive functioning, whilst acknowledging important areas of distinction, such as developmental course and association with epilepsy (Owen, O'Donovan, Thapar & Craddock, 2011; Rutter, 2013). The disorders share a number of clinical features and researchers continue to search for evidence of

aetiological commonality underlying such shared features (Stone & Iguchi, 2011). Investigations have been carried out on a number of levels: (i) clinical symptomatology, (ii) neurobiology, and (iii) genes (Stone & Iguchi, 2011).

There is considerable overlap in symptomatology between the two disorders, for example, social withdrawal, flattening of affect, oddness, restricted interests and disordered thinking (Sasson, Pinkham, Carpenter & Belger, 2011). In particular, social cognitive deficits, such as impaired 'theory of mind', are a key feature of both conditions (Craig, Hatton, Craig & Bentall, 2004).

Research in both fields has sought to discover shared neurobiology which may underlie such clinical symptoms, however the evidence remains equivocal (Stone & Iguchi, 2011). Cheung et al. (2010) reviewed literature relating to the brain anatomical phenotype of ASD and schizophrenia, as assessed by neuroimaging findings. Whilst they found areas of considerable overlap between the two disorders in terms of brain volume as compared to controls (e.g. low volume of grey matter in limbic-striato-thalamic circuits), there were also areas of clear distinction, for example grey matter deficit in the left putamen in ASD and deficits in the amygdala for schizophrenia (Cheung et al., 2010).

Twin studies suggest that both schizophrenia and ASD carry a significant genetic component in their aetiology (Stone & Iguchi, 2011). There is also evidence that these disorders share common genetic susceptibility factors, for example, Copy Number Variations (CNVs; submicroscopic chromosomal deletions or duplications which can result in an increase or decrease in gene expression) at specific locations have been found to be associated with both ASD and schizophrenia (Burbach & van der Zwaag, 2009; Cook & Scherer, 2008; International Schizophrenia Consortium, 2008). Studies report finding recurrent CNVs in the same chromosomal regions and

single genes in both individuals with autism and in those with schizophrenia (e.g. the 1q21.1, 15q11.2 and 15q13.3 regions, Burbach & van der Zwaag, 2009). However, other studies estimate the overlap in such genetic processes to be modest, suggesting that, whilst reciprocal variants constitute risk factors for both conditions, they manifest differently in the two disorders (Crespi, Stead & Elliot, 2010).

Research continues to investigate whether comorbidity reflects common underlying causality, whether each condition represents an alternate form of the same disorder, or whether these populations represent distinct groups that happen to share the same surface attributes.

Recent studies suggest that adults, as well as children, with ASD have high rates of psychiatric comorbidity (Joshi et al., 2013). However, research into the prevalence of psychosis in an adult ASD population has been somewhat neglected and the evidence that does exist appears to be equivocal (Davidson, Greenwood, Stansfield & Wright, 2013). It is important for clinicians working with an ASD population to understand whether the difficulties associated with ASD convey a particular risk of developing psychosis and to consider the possibility of comorbid psychotic disorders rather than misattributing symptoms of psychosis to ASD. Such misattribution may deprive the individual of the possibility of receiving specific treatment appropriate to psychosis and, in particular, access to early evidence-based intervention as recommended by NICE guidelines (2014). Conversely, there is also the risk of clinicians mistaking the unusual, restricted interests associated with ASD for psychotic delusions (Dossetor, 2007), which could result in the administration of inappropriate medications with significant side effect profiles. In addition, clinicians working in psychosis services report individuals attending the clinic who appear to present with features of ASD but have not been diagnosed with the disorder

(Davidson et al., 2013). Diagnosis of ASD is important in enabling individuals to access vital targeted support from health and social services since many adults with ASD suffer exclusion both socially and economically (NICE, 2012).

Aims of this review

Gaining a clearer understanding of the likelihood of co-occurrence of ASD and psychosis is important in informing best clinical practice and in guiding future research into areas of commonality and difference and into effective treatments for individuals who experience comorbidity. Thus, this review aimed to tackle limitations in the ASD and psychosis literature by examining: (1) research into the prevalence of psychosis in individuals diagnosed with ASD and (2) research into the prevalence of ASD in individuals diagnosed with a psychotic disorder, with a view to discovering whether, according to current evidence, such prevalence in each case may be higher than in the general population.

Method

Search strategy

A systematic search of the PsychINFO and Ovid MEDLINE computerised databases was undertaken from database inception to 15 September 2014 (see Appendix A for details). The terms *autis**, *ASD*, *asperger**, *pervasive developmental disorder* or *PDD* were combined with *psychosis*, *psychotic* or *schizophren** in a search of titles, abstracts and keywords of studies entered in these databases. In addition, medical subject headings were searched. The search results were limited to English language and human subjects. The reference lists of the included papers were also searched by hand.

Inclusion criteria

This review included studies meeting the following criteria: (1) the target population included adults (aged 18 or over); (2) the sample included individuals with an IQ (full-scale or estimated) of 70 or above; (3) the article reported on the prevalence of comorbid psychotic disorders in individuals diagnosed with an ASD, or on the prevalence of comorbid ASD in individuals diagnosed with a psychotic disorder; (4) the article reported an original piece of research; (5) the study was published in a peer-reviewed journal; (6) the study was published between January 1994 and September 2014. Studies meeting these criteria were formally assessed for quality and relevance.

The review was limited to studies published after 1994. This study period was selected because 1994 is the year that DSM-IV was published (APA) and that ICD-10 (World Health Organisation [WHO], 1992) came into use in World Health Organisation member states (WHO, 2015). Diagnostic criteria for ASD have varied considerably over the years but by 1994 a degree of consensus had been achieved in conceptualising autism as a spectrum of developmental disorders. DSM-IV and ICD-10 describe similar subgroups of disorder within the spectrum (Wing & Potter, 2002) and cases diagnosed according to these principles show a high degree of correspondence to individuals diagnosed under current criteria (e.g., Huerta, Bishop, Duncan, Hus & Lord, 2012). Studies published prior to 1994 would have relied on somewhat different diagnostic criteria thus limiting the generalizability of findings to current conceptualisations of ASD.

For the purposes of this review Autism Spectrum Disorders includes any of the previously distinct ASD diagnoses described in DSM-IV (APA, 1994): autistic disorder, Asperger's disorder, childhood disintegrative disorder and pervasive

developmental disorder not otherwise specified (PDD-NOS). This is consistent with the approach to diagnostic criteria adopted by DSM-5 (APA, 2013a), which reflects research suggesting a single overarching disorder is a more accurate and useful way of conceptualising this spectrum of difficulties (APA, 2013b).

The definition of "psychosis" in this review is fairly broad, encompassing the schizophrenia spectrum and other psychotic disorders set out in DSM-5 (APA, 2013a), as well as unipolar or bipolar mood disorders where psychotic symptoms are expressly stated to coexist. This definition reflects the broader end of the range of psychotic disorders reported in the literature (e.g. Davidson et al., 2013).

Childhood-onset schizophrenia (COS), in which symptoms appear before 13 years of age, is considered extremely rare, with a prevalence of approximately 1 in 40,000, equating to around 0.025 cases per 1000 persons (Gochman, Miller & Rapoport, 2011), as opposed to an estimated lifetime prevalence of adolescent or adult onset schizophrenia (AOS) of approximately 4 per 1000 (e.g. Saha, Chant, Welham & McGrath, 2005). COS is hypothesised to constitute a more severe form of the disorder, with studies suggesting COS is associated with greater brain morphologic abnormality, more severe neurobehavioural difficulties and greater genetic risk than AOS (e.g. Sowell, Toga & Asarnow, 2000). In addition, the slight developmental delays observed in prospective cohort studies of AOS appear to be heightened in individuals with COS, with a substantial proportion of children with COS observed to manifest significant developmental abnormalities of communication and social relatedness consistent with a diagnosis of ASD (Rapoport, Chavez, Greenstein, Addington & Gogtay, 2009). In view of these subtle distinctions between COS and AOS it was decided to exclude studies reporting on COS from this review. This review focuses primarily on the co-occurrence ASD and

psychotic disorders in adults, although where studies included both adults and adolescents these were retained.

In this review the term "learning disability" refers to individuals with an IQ below 70. An IQ is stated to be in the "normal range" for individuals with an IQ of 70 or more. This review aimed to assess the occurrence of comorbid ASD and psychotic disorders in individuals across the range of intellect rather than specifically in adults with a learning disability. As such, studies in which every participant met criteria for a learning disability were not included.

Results

The PsychINFO and Ovid MEDLINE searches identified 3982 studies (after deduplication), of which 2729 were within the specified date range. Abstracts of these studies were screened according to the inclusion criteria. Twenty studies met criteria (1) to (5) above and were subjected to formal quality assessment. Reasons for exclusion included: genetic or physiological studies, review or conceptual papers, studies reporting on prevalence of ASD or psychotic traits rather than of cases meeting diagnostic criteria, case reports and studies in which the sample consisted entirely of children or individuals with a learning disability. In the current project, the resources were not available for two researchers to apply inclusion criteria to papers identified in the search, and to then assess the level of consensus.

Quality and relevance assessment

Quality of studies was assessed using a checklist developed by Hoy et al. (2012) for assessing risk of bias in prevalence studies. Whilst there are numerous instruments designed to assess experimental studies, the use of tools to assess observational studies in systematic reviews is less established (Mallen, Peat & Croft, 2006). In a recent review of quality appraisal tools applicable to studies examining

prevalence of diseases, Shamliyan, Kane and Dickinson (2010) found existing scales and checklists to vary widely and to fall short in a number of key areas: discrimination of poor study reporting from methodological quality, distinction between internal and external validity and a lack of consistency in terms of reporting on tool development as well as reliability. The authors also noted that most numerical scales, where particular weight is allocated to certain items, appeared arbitrary (Shamliyan et al., 2010). In response to this, Hoy et al. (2012) sought to develop a rigorous risk of bias tool for prevalence studies by reviewing the existing literature, establishing expert consensus and by testing the finalised tool for inter-rater reliability.

The Risk of Bias tool (ROBT, Hoy et al., 2012; see Appendix B) consists of 4 questions relating to external validity: (1) representativeness of target population; (2) representativeness of sampling frame; (3) use of random selection; (4) non-response bias; and 6 questions relating to internal validity: (5) direct collection of data; (6) acceptable case definition; (7) reliability and validity of study instruments established; (8) same mode of data collection used for all participants; (9) appropriate length of shortest prevalence period; (10) correct reporting of numerator and denominator (Hoy et al., 2012). Question (9) was considered less relevant to this review on the basis that ASD is a lifelong developmental disorder and that appropriate assessment of psychotic disorders is more important in than the shortest prevalence period.

Each study is rated as 'high' or 'low' risk of bias in relation to each of the nine questions referred to above. On the basis of these ratings the rater provides an overall summary rating for each study, as being subject to low, moderate or high risk of bias. Hoy and colleagues reported 93% agreement between raters on the 10

individual items of the tool and moderate agreement on the overall rating of studies. A summary rating for each included study is presented in Tables 1 and 2.

Prevalence of psychotic disorders in individuals diagnosed with ASD

Fourteen studies were included (Table 1), with occurrence of psychosis in ASD in ranging from 0% (Ghaziudin, Weidmer-Mikhail & Ghaziudin, 1998; Hutton, Goode, Murphy, Le Couteur & Rutter, 2008) to 61.5% (Raja & Azzoni, 2010).

Type of prevalence. Studies varied as to the temporal criteria applied when estimating prevalence. Five papers estimated prevalence of psychosis across the individual's lifetime (Buck et al., 2014; Hofvander et al., 2009; Joshi et al., 2013; Larsen & Mouridsen, 1997; Mouridsen, Rich, Isager & Nedergaard, 2008), with estimates ranging from 5.6% to 34.8%. Three studies reported prevalence of psychosis at a particular point in time, for example, at time of assessment (Buck et al., 2014; Joshi et al., 2013) or at time of discharge (Russell, Mataix-Cols, Anson, & Murphy, 2005). Estimates of point prevalence ranged from 5% to 8%. Five studies reported period prevalence of psychosis, including occurrence during a specified period preceding or following assessment (Ghaziudin & Zafar, 2008; Ghaziudin et al., 1998), occurrence during the period since participants first received their diagnosis of ASD (Hutton et al., 2008) or, in two cases, during an unspecified period of time (Kohane et al., 2012; Raja & Azzoni, 2010). Estimates of period prevalence in these studies varied from 0% to 61.5%. In three cases it was not clear which temporal criteria were applied when estimating prevalence, which ranged from 4% to 16% (Billstedt, Gillberg & Gillberg, 2005; Lugengard, Hallerbäck & Gillberg, 2011; Stahlberg, Soderstrom, Rastam & Gillberg, 2004).

Definition of caseness. Definitions of "psychosis" in these studies varied. Two papers specifically stated that no cases of "schizophrenia" were reported

(according to ICD-10, Hutton et al., 2008, and DSM-III and DSM-IV, Ghaziudin et al., 1998). Others appeared to assess for any of a spectrum of psychotic disorders under ICD or DSM (e.g. Kohane et al., 2012; Mouridsen et al., 2008). One study (Stahlberg et al., 2004) referred expressly to the occurrence of bipolar disorder with psychotic features and these cases are included in the reported prevalence rates, whereas other studies reported diagnoses of bipolar disorder but made no mention of whether such presentation was accompanied by psychotic features (e.g. Joshi et al., 2013). Billstedt and colleagues (2005) refer broadly to psychosis as diagnosed by a psychiatrist, without reference to any diagnostic criteria.

Case ascertainment. Ascertainment of psychosis cases was carried out by a variety of methods, ranging from case note review without any face-to-face contact, to clinical interview of the individual being assessed with the aid of a structured diagnostic tool. Several studies referred to multiple sources of available information in their case ascertainment (e.g. clinical status of the individual, structured interview, DSM-IV criteria checklist and informant semi-structured collateral interview, Stahlberg et al., 2004). The Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I; First, Gibbon, Williams & Spitzer, 1997) was employed in four studies (Hofvander et al., 2009; Joshi et al., 2013; Lugnegard et al., 2011; Stahlberg et al., 2004). Raja and Azzoni (2010) employed the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983) and the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984). Hofvander et al. (2009) reported using a structured DSM-IV based clinical interview to assess participants. Other studies ascertained psychosis cases by means of an informant interview, including with the aid of a structured instrument specifically designed to assess psychiatric disorders in individuals with developmental difficulties. Buck et al. (2014) used an

abbreviated version of the Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD; Moss et al., 1998) and Hutton et al. (2008) utilised the Schedule for Assessment of Psychiatric Problems Associated with Autism (SAPPA; Bradley & Bolton, 2006). Several studies reported carrying out a psychiatric examination of the individual being assessed and/or a collateral informant interview but did not employ a structured instrument in this process (Billstedt et al., 2005; Ghaziudin and Zafar, 2008; Ghaziudin et al., 1998), although Ghaziudin et al. (1998) do report utilising symptom checklists for DSM-III and DSM-IV. Four studies did not carry out any direct assessment of individuals or informants but employed various methods of record review: hospital records (Kohane et al., 2012), medical records of psychiatric inpatient admissions (Larsen & Mouridsen, 1997), records on a national psychiatric register regarding admissions and consultations (Mouridsen et al., 2008) and admission and discharge reports (Russell et al., 2005).

Sampling methods. Two studies collected data in the community (Billstedt et al., 2005; Buck et al., 2014) and two via multiple institutions (Hofvander et al., 2009 and Kohane et al., 2012). The majority of included studies recruited their samples via one or two specialist ASD or neuropsychiatric clinics (Ghaziudin & Zafar, 2008; Ghaziudin et al., 1998; Hutton et al., 2008; Joshi et al., 2013; Lugnegard et al., 2011; Russell et al., 2005; Stahlberg et al., 2004). Two studies (Larsen & Mouridsen, 1997; Mouridsen et al., 2008) collected data in psychiatric clinics and one study (Raja & Azzoni, 2010) in a psychiatric intensive care unit.

Table 1

Summary table of reviewed studies reporting occurrence of psychosis in ASD

Study	n	Country	Sample	IQ	Method of assessing ASD and (diagnostic criteria)	Method of assessing psychosis and (diagnostic criteria)	Prevalence (temporal criteria)	Risk of bias
Hofvander et al., 2009*	122	Sweden and France	Two child neuropsychiatric clinics One psychiatric outpatient clinic	Normal range	Record review, informant interview where possible, clinical assessment (DSM-IV / Gillberg & Gillberg (1989) criteria for AS)	SCID-I or Structured, DSM-IV-based, clinical interview plus life-time DSM-IV symptom checklist (DSM-IV)	12% (lifetime prevalence)	Low
Joshi et al., 2013	63	USA	ASD clinic	Mixed	Neuropsychological assessment, structured diagnostic interview, structured diagnostic interview of primary caretaker if available. (DSM-IV)	SCID-I administered to individual and informant where available (DSM-IV)	8% (status at time of assessment) 13% (lifetime prevalence)	Low
Stahlberg et al., 2004*	129	Sweden	Child neuropsychiatric clinic	Mixed	Diagnoses based on all available information, including clinical status of the patient, ASSQ, ASDI, and DSM-IV criteria checklist. Where possible, informant semi-structured collateral interview.	Diagnoses based on all available information, including clinical status of the patient, SCID-1 and DSM-IV criteria checklist. Where possible, informant semi-structured collateral interview.	7% prevalence of bipolar disorder with psychotic features 7.8% prevalence of schizophrenia or another psychotic disorder (ns)	Low
Billstedt et al., 2005	108	Sweden	Community	Mixed	DISCO and/or record review (DSM-IV / ICD-10)	Psychiatric examination and/or interview with informant (ns)	7% in autistic disorder group 9% in atypical autism group (ns)	Medium

Study	n	Country	Sample	IQ	Method of assessing ASD and (diagnostic criteria)	Method of assessing psychosis and (diagnostic criteria)	Outcome	Risk of bias
Buck et al., 2014	129	USA	Community	Mixed	Record review, historical and present symptom forms, current mental state examination and family interview (DSM-III) Record review (DSM-IV)	Mini PAS-ADD informant interview (ICD-10)	5% (status at time of assessment) 10% (lifetime prevalence)	Medium
Hutton et al., 2008	135	UK	ASD clinic	Mixed	ADI-R and ADOS (ns)	Telephone screen with informant SAPPA informant interview (ICD-10)	0% (over period since ASD first diagnosed)	Medium
Ghaziuddin & Zafar, 2008	28	USA	ASD clinic	ns	Record review, neuropsychological assessment, speech and language evaluation, psychiatric interview, ABC completed by informant (DSM-IV)	Psychiatric interview and chart review (DSM-IV)	7.1% (status at time of assessment or during previous 12 months)	High
Ghaziuddin et al., 1998	35	USA	ASD clinic	Normal range	Diagnosis according to ICD-10 / DSM-IV criteria (ICD-10 / DSM-IV)	K-SADS-E for participants below 17 years of age, record review, psychiatric examination, symptom checklists (DSM-III / DSM-IV)	0% prevalence (status at time of assessment or during 2 year follow-up period)	High
Kohane et al., 2012	ns**	USA	Three general hospitals, one paediatric hospital	ns	Retrospective hospital record review, using Shared Health Research Informatics Network software, not chart review (ICD-9 as used by healthcare providers for billing)	Retrospective hospital record review, not chart review (ICD-9 as used by healthcare providers for billing)	8.8% (period ns)	High

Study	n	Country	Sample	IQ	Method of assessing ASD and (diagnostic criteria)	Method of assessing psychosis and (diagnostic criteria)	Outcome	Risk of bias
Larsen & Mouridsen, 1997	18	Denmark	Child psychiatric hospitals	Mixed	Child psychiatric record review (ICD-10)	Medical case records of individuals admitted to adult psychiatric departments (ICD-10)	5.6% (lifetime prevalence)	High
Lugnegard et al., 2011	54	Sweden	Two neuropsychiatric clinics	Normal range	DISCO-11 (ns)	SCID-I (DSM-IV)	4% (ns)	High
Mouridsen et al., 2008	89	Denmark	Two child psychiatric clinics	Mixed	Psychiatric record review (ICD-10)	Data extracted from nationwide Danish Psychiatric Central Register for inpatient admissions and outpatient consultations (ICD-10)	34.8% (lifetime prevalence)	High
Raja & Azzoni, 2010	26	Italy	Psychiatric intensive care unit	Mixed	Clinical diagnosis based on record review and informant interview (DSM-IV-TR)	SAPS and SANS (DSM-IV-TR)	61.5% (period ns)	High
Russell et al., 2005	40	UK	Specialist ASD clinic	Normal range	ADI (where parent available) Psychiatric assessment (ICD-10)	Admission / discharge reports review (ICD-10)	7.5% (status at time of discharge)	High

Note. ABC = Autism Behavior Checklist (Krug, Arick & Almond, 1980); ADI-R = Autism Diagnostic Interview-Revised (Lord, Rutter & Le Couteur, 1994); ADOS = Autism Diagnostic Observation Schedule (Lord et al., 2000); ASDI = Asperger Syndrome Diagnostic Interview (Gillberg, Gillberg, Rastam & Wentz, 2001); ASSQ = the Asperger Syndrome and high functioning autism Screening Questionnaire (Ehlers & Gillberg, 1993); DISCO = Diagnostic Interview for Social and Communication Disorders (Wing, Leekam, Libby, Gould & Larcombe, 2002); K-SADS-E = Kiddie-Schedule for Affective Disorders and Schizophrenia – Epidemiological Version (Puig-Antich, Orvaschel, Tabrizi & Chambers, 1980); PAS-ADD = Psychiatric Assessment Schedule for Adults with Developmental Disability (Moss et al., 1998); SANS = Scale for Assessment of Negative Symptoms (Andreasen, 1983); SAPPA = Schedule for Assessment of Psychiatric Problems Associated with Autism (Bradley& Bolton, 2006); SAPS = Scale for Assessment of Positive Symptoms (Andreasen, 1984); SCID = Structured Clinical Interview for DSM-IV Axis I disorders (First, et al., 1997).

***** Some participants in Hofvander et al. (2009) were also studied in Stahlberg et al. (2004)

** Total sample in Kohane et al. (2012) was 14,381, which includes adults and children. Outcome figures reported here are for adults only.

Method of assessing ASD. All studies specify formal diagnostic criteria employed when diagnosing ASD, most commonly, DSM-IV (APA, 1994) and ICD-10 (WHO, 1992), save for two (Hutton et al., 2008 and Lugnegard et al., 2011), both of which use diagnostic measures based on ICD-10 or DSM-IV criteria. Three studies employed validated diagnostic measures approved by NICE (2012) as having sufficient psychometric evidence to recommend their use in assessing ASD in adult populations: Hutton et al. (2008) used the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) and the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), Russell et al. (2005) also used the ADI-R, where an informant was available, and Stahlberg et al. (2004) employed the Asperger Syndrome Diagnostic Interview (ASDI; Gillberg et al., 2001). Other studies utilise instruments which are not NICE recommended for use with adults due to lack of psychometric evidence but are widely used in the clinic, for example, the Diagnostic Interview for Social and Communication Disorders (DISCO; Wing et al., 2002) employed by Billstedt et al. (2005) and Lugnegard et al. (2011). Three papers state that a neuropsychological or clinical assessment was carried out but do not stipulate use of a particular measure (Ghaziudin & Zafar, 2008; Hofvander et al., 2009; Joshi et al., 2013). Ten studies report involving a family member or other informant in the assessment process, where possible, as recommended by NICE (2012) guidelines (Billstedt et al., 2005; Buck et al., 2014; Ghaziuddin & Zafar, 2008; Hofvander et al., 2009; Hutton et al., 2008; Joshi et al., 2013; Lugnegard et al., 2011; Raja & Azzoni, 2010; Russell et al., 2005; Stahlberg et al., 2004). Three studies rely solely on record reviews in conjunction with diagnostic criteria: Kohane et al., 2012; Larsen & Mouridsen, 1997; Mouridsen et al., 2008). Several papers use a combination of the methods referred to

above, drawing on multiple sources of available data (e.g. Hofvander et al., 2009; Stahlberg et al., 2004).

Prevalence of ASD in individuals diagnosed with psychotic disorders

Six studies reported on prevalence of ASD in a population of individuals diagnosed with psychosis (Table 2). Occurrence of ASD in psychosis ranged from 0.8% (Chang et al., 2003) to 27% (Hallerback, Lugnegard & Gillberg, 2012).

Type of prevalence. Whereas the course of psychosis may extend over a period ranging from weeks to decades, ASD is considered a lifelong developmental disorder. Prevalence estimates in these studies reflect this and, in general, do not distinguish between point, period and lifetime prevalence.

Definition of caseness. All studies (excluding Mandell et al., 2012) reference specific diagnostic criteria applied in identifying ASD cases. Three studies apply DSM-IV criteria (Chang et al., 2003; Davidson et al., 2013; Fraser et al., 2012) and two studies utilise ICD-10 criteria (Hallerback et al., 2012; Nylander & Gillberg (2001). Gillberg's criteria for Asperger Syndrome (Leekam et al., 2000) are also referenced by a number of studies (e.g. Hallerback et al., 2012). Studies varied as to the precise diagnostic categories included in their research. Both Chang et al. (2003) and Fraser et al. (2012) use DSM-IV pervasive developmental disorder diagnoses, however, the latter authors exclude Rett's Disorder and Childhood Disintegrative Disorder. Hallerback et al. (2012) and Nylander and Gillberg (2001) apply ICD-10 criteria for diagnoses of childhood autism and atypical autism but prefer Gillberg's criteria for Asperger syndrome (AS; Hallerback al., 2012) or diagnose individuals meeting ICD-10 criteria for AS with "ASD" (Nylander & Gillberg, 2001). Davidson et al.'s (2013) study focuses exclusively on identifying cases of AS. Mandell et al.

(2012) do not provide a clear definition of ASD although do state that the ADI-R diagnostic algorithm (based on ICD-10 and DSM-IV guidelines, Lord et al., 1994) is utilised in some cases.

Table 2
Summary table of reviewed studies reporting occurrence of ASD in psychosis

Study	n	Country	Sample	IQ	Method of assessing psychosis and (diagnostic criteria)	Method of assessing ASD and (diagnostic criteria)	Prevalence	Risk of bias
Hallerback et al., 2012	44	Sweden	Adult psychiatric clinic	Normal range	SCID-I (DSM-IV)	DISCO-11 interview with informant, AQ, patient record review (ICD-10)	27%	Medium
Mandell et al., 2012	123	USA	Inpatient psychiatric hospital	Mixed	SANS-SAPS, review of historical charts and electronic records using a semi-structured abstraction process, case conference (ns)	ADI-R interview with informant (only possible in 61 cases), review of historical charts and electronic records using a semi-structured abstraction process, SRS, case conference (ns)	9.8%	Medium
Nylander and Gillberg, 2001	423	Sweden	Psychiatric outpatient clinic	Mixed	Record review (ICD-9)	ASDASQ completed by the primary clinician, record review, participant interview, informant interview including ASSQ and ASDI (ICD-10)	1.7%	Medium
Chang et al., 2003	128	Taiwan	Adult psychiatric outpatient clinic	Mixed	ns (DSM-IV)	ASDASQ, individual and informant interview (DSM-IV)	0.8%	High
Davidson et al., 2013	197	UK	Early Intervention in Psychosis Service	Normal range	SCI-PANSS (ICD-10)	ASDASQ, case note review, diagnostic interview (DSM-IV)	3.6%	High

Study	n	Country	Sample	IQ	Method of assessing psychosis and (diagnostic criteria)	Method of assessing ASD and (diagnostic criteria)	Prevalence	Risk of bias
Fraser et al., 2012	292	Australia	Youth mental health service	ns*	ns (ns)	Treating clinician asked to classify participant as having been diagnosed with ASD by psychiatrist, paediatrician or clinical psychologist (based on all available records) (DSM-IV)	3.4%	High

Note. ADI-R = Autism Diagnostic Interview-Revised (Lord et al., 1994); AQ = Autism-Spectrum Quotient (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001); ASDASQ = Autism Spectrum Disorder in Adults Screening Questionnaire (Nylander & Gillberg, 2001); ASDI = Asperger Syndrome Diagnostic Interview (Gillberg et al., 2001); DISCO = Diagnostic Interview for Social and Communication Disorders (Wing et al., 2002); SANS = Scale for Assessment of Negative Symptoms (Andreasen, 1983); SAPS = Scale for Assessment of Positive Symptoms (Andreasen, 1984); SCID = Structured Clinical Interview for DSM-IV Axis I disorders (First, et al., 1997); SCI-PANSS = Structured Clinical Interview for Positive and Negative Syndrome Scale (Kay, Fiszbein & Opfer, 1987); SRS = Social Responsiveness Scale (Constantino, 2005).
* Participant IQ not stated in Fraser et al. (2012), however service sampled is stated not to be resourced to cope with moderate or severe LD.

Case ascertainment. Two studies employed validated informant report measures recommended by NICE for the assessment and diagnosis of ASD in adults (although in both studies this was dependent upon an informant being available for interview): the ADI-R (Lord et al., 1994) was used by Mandell and colleagues (2012) and the Asperger Syndrome Diagnostic Interview (ASDI; Gillberg et al., 2001) was used by Nylander and Gillberg (2001). One study (Hallerback et al., 2012) used a case identification instrument approved by NICE for the identification of ASD in individuals with IQ in the normal range, the Autism-Spectrum Quotient (AQ; Baron-Cohen et al., 2001). Hallerback and colleagues (2012) also used an adapted form of the DISCO-11 (Wing et al., 2002) to interview parents where possible, a measure which is not recommended by NICE for the diagnosis of ASD in adults but is widely used by clinicians. Three studies engaged in a screening process prior to employing formal diagnostic techniques to assess for ASD, by means of the Autism Spectrum Disorder in Adults Screening Questionnaire (ASDASQ; Nylander & Gillberg, 2001) in the case of Chang et al. (2003), Davidson et al. (2013) and Nylander and Gillberg (2001) and, additionally, by means of a case note review in Davidson et al., 2013 and Nylander and Gillberg (2001). Fraser et al. (2012) ascertained cases by asking the primary clinician treating the individual's psychiatric difficulties to classify individuals as falling within DSM-IV diagnostic criteria or not. None of the included studies reported employing observational tools (e.g. the ADOS; Lord et al., 2000) in their ascertainment of cases.

Sampling methods. All the studies recruited their samples in single clinics treating individuals for mental health difficulties, excluding Fraser et al. (2012) where data were collected across several clinics making up a broader mental health service.

Method of assessing psychosis. Two studies did not stipulate diagnostic criteria applied in identifying psychosis cases (Fraser et al., 2012; Mandell et al., 2012). Other studies reported reference to DSM-IV (Chang et al., 2003; Hallerback et al., 2012), ICD-10 (Davidson et al., 2013) or ICD-9 (Nylander & Gillberg, 2001). Three studies report employing structured diagnostic tools in a face-to-face diagnostic process when assessing for psychosis. Davidson et al. (2013) used the Structured Clinical Interview for Positive and Negative Syndrome Scale (SCI-PANSS; Kay et al., 1987) and describe the broad definition of psychosis adopted by the service sampled: all non-organic psychotic disorders in ICD-10 and unipolar or bipolar mood disorders where psychotic symptoms are present. Hallerback et al. (2012) used the SCID-I (First et al., 1997) and report a broad range of SCID psychosis subtypes including Bipolar disorder type I. Mandell et al. (2012) employed the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983) and the Scale for Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and report diagnoses of schizophrenia, including psychosis not otherwise specified. Three remaining studies do not describe the process by which a diagnosis is reached at the particular clinics sampled: Chang et al. (2003) report initial psychiatric diagnoses of schizophrenia according to DSM-IV. Fraser et al. (2012) simply describe a diagnostic category of "psychosis" (p. 85). Nylander and Gillberg (2001) refer to registered diagnoses according to ICD-9, grouped as: schizophrenia or paranoid psychosis, acute non-affective psychosis, cycloid psychosis and affective psychosis.

Discussion

This review aimed to investigate existing literature estimating the co-occurrence of ASD and psychosis and to assess whether: (i) the prevalence of

psychosis may be higher in an ASD population than in the general population; and (ii) whether the prevalence of ASD maybe in higher in a psychosis population than in the general population. Current estimates of prevalence of ASD in the general population are approximately 1% in both child and adult populations (DSM-5; APA, 2013a; Baron-Cohen et al., 2009; Brugha et al., 2012). Such estimates represent an increase on rates reported in the 1970s when childhood autism was thought to affect only 0.04% of individuals (e.g. Rutter, 1978). There is uncertainty as to whether contemporary estimates of prevalence reflect the broadening of diagnostic criteria, greater awareness of the condition, an improvement in methods of diagnosis or a genuine increase in the prevalence of ASD (DSM-5; APA, 2013a). There is also a history of variability in the estimated prevalence of schizophrenia in the general population. DSM-IV (APA, 1994) notes that large studies have estimated prevalence as ranging from 0.2% to 2% and concludes lifetime prevalence of schizophrenia as lying between 0.5% and 1%. More recently, DSM-5 (APA, 2013a) reduced this estimate of lifetime prevalence to between 0.3% and 0.7%.

The present review found extensive variability in the reported estimates of prevalence of psychosis in ASD, ranging from 0% to 61.5% and highlights the heterogeneity of studies attempting to investigate this issue. The studies varied widely in terms of both external and internal validity, with differences in sampling frame, size of sample, case definition, approach to diagnosis and method of data collection. Quality appraisal suggests that around two thirds of the included studies may have a moderate to high risk of bias in estimating the prevalence of psychosis in this population.

Four studies utilising community or multiple clinic samples and benefitting from somewhat larger sample sizes report prevalence (other than point prevalence)

ranging from 8.8% to 16% (Billstedt et al., 2005; Buck et al., 2014; Hofvander et al., 2009; Kohane et al., 2012). Of these, only two studies stipulate the specific type of prevalence reported (Buck et al., 2014; Hofvander et al., 2009) with both studies estimating lifetime prevalence and reporting rates of 10% and 12% respectively. One of these two studies (Hofvander et al., 2009) was considered to have made significant attempts to minimise bias such that there was estimated to be a low risk of bias associated with this study. Buck et al. (2014), thought to have a medium risk of bias, also provide a point prevalence estimate of 5%.

Other studies recruited participants from one or two ASD or neuropsychiatric clinics and tended to have smaller sample sizes. Three such studies reported lifetime prevalence estimates of: 5.6% (Larsen & Mouridsen, 1997; ascertaining cases via record review and utilising a very small sample size, therefore assessed as having a high risk of bias), 13% (Joshi et al., 2013; thought to have a low risk of bias) and 34.8% (Mouridsen et al., 2008; consisting of a record review and assessed as incorporating a high risk of bias). Three studies recruiting from one or two clinics reported a range of period prevalence estimates: 0% over the period since first receiving an ASD diagnosis (Hutton et al., 2008; assessed as having a medium risk of bias), 0% at time of assessment and over a two year follow-up period (Ghaziudin et al., 1998; considered to have a high risk of bias) and 7.1% at time of assessment and during the previous twelve months (Ghaziudin & Zafar, 2008; also associated with a high risk of bias). Two studies reported similar point prevalence estimates of 7.5% (Russell et al., 2005; thought to have a high risk of bias) and 8% (Joshi et al., 2013; assessed as low risk in terms of bias). Two further such studies reported prevalence estimates without stating the type of prevalence investigated: 4% (Lugnegard et al., 2011) and 7.8% (or, 14.8% including bipolar disorder with

psychotic features; Stahlberg et al., 2004). Whilst the overall risk of bias in Stahlberg et al. (2004) was assessed as being relatively low, the quality of reporting in this study would have benefitted from an express statement as to the type of prevalence estimated (i.e. point, period or lifetime).

One study (Raja & Azzoni, 2010), reporting a much higher estimate of prevalence than the other studies included here (61.5% prevalence over a period which was not specified), sampled a Psychiatric Intensive Care Unit. This study was considered to be associated with a particularly high risk of bias given the highly selected nature of this sample in a care setting designed specifically for complex, comorbid cases.

Studies utilising structured diagnostic tools for the ascertainment of psychosis cases reported lifetime prevalence estimates of 12% (Hofvander et al., 2009; SCID-I) and 13% (Joshi et al., 2013; SCID-I). Other studies utilising such tools did not stipulate the type of prevalence reported and provided estimates of 4% (Lugnegard et al., 2011; SCID-I), 61.5% (Raja & Azzoni, 2010; SAPS and SANS) and 14.8%, including bipolar disorder with psychotic features, (Stahlberg et al., 2004; SCID-I).

Assessment of psychosis usually involves direct interaction with the individual concerned (NICE, 2014), however two studies utilised structured informant interview tools as a means of ascertaining cases of psychosis. Buck et al. (2014), using the Mini PAS-ADD informant interview, estimated lifetime prevalence of psychosis to be 10% and Hutton et al. (2008), utilising the SAPPA, estimated the occurrence of psychosis over the period since ASD was first diagnosed to be 0%. Both these studies recruited individuals with learning difficulties as well as individuals assessed as having an IQ in the normal range. However, the tools utilised in these studies were designed specifically for use with individuals with learning

difficulties (Mini PAS-ADD, see Buck et al., 2014; SAPPA, see Bradley & Bolton, 2006) and have not been validated in individuals with normal IQ.

Other studies used a variety of methods of case ascertainment widely employed in the clinic, including psychiatric examination, collateral interview with informant and symptom checklists based on diagnostic criteria. Estimates of prevalence were 1 year period prevalence of 0% (Ghaziuddin et al., 1998; assessed as having a high risk of bias), 2 year period prevalence of 7.1% (Ghaziuddin & Zafar, 2008; also thought to have a high risk of bias) and a non-specific prevalence of 16% (Billstedt et al., 2005; associated with a medium risk of bias).

All studies ascertaining caseness by means of a record review process were assessed as being associated with a high risk of bias (Kohane et al., 2012; Larsen & Mouridsen, 1997; Mouridsen et al., 2008; Russell et al., 2005). Estimates reported ranged from 5.6% to 34.8%.

Based on studies which appear to have the lowest risk of bias and appropriately report the type of prevalence estimated, the lifetime prevalence of psychosis in an adult ASD population might be estimated to be around 12-13% (e.g. Hofvander et al., 2009; Joshi et al., 2013). This estimate is significantly higher than the lifetime prevalence estimate of schizophrenia in the general population reported by DSM-5 (APA, 2013a) of between 0.3% and 0.7%.

The studies reviewed here reporting on estimated occurrence of ASD in psychosis also reveal considerable variability, with prevalence estimates ranging from 0.8% to 27%. All of the studies sampled single psychiatric clinics or services rather than selecting samples from the community. Definitions of ASD varied greatly across studies, with different diagnostic frameworks being applied (DSM-IV, ICD-10, Gillberg's criteria for AS) and studies setting different inclusion criteria in

terms of ASD diagnosis sought. For example, Davidson et al. (2013) aim exclusively to identify cases of Asperger's Disorder (according to DSM-IV criteria) and estimate prevalence of 3.6% in their Early Intervention in Psychosis Service sample. They suggest this may be a conservative estimate in view of the screening process employed prior to engaging in more thorough assessment. However, Davidson et al.'s (2013) psychosis population is somewhat broader than that of other studies, including unipolar or bipolar mood disorders where psychotic symptoms are present. Chang et al. (2003) apply broader ASD criteria, including DSM-IV diagnoses of autism, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder and PDD-NOS. Their estimate of prevalence is substantially lower than that of Davidson and colleagues (2013) at only 0.8%. Again, there are concerns as to the screening process adopted by Chang et al. (2003) and the lack of validated instrument employed in the final stages of case ascertainment.

As previously discussed, only two studies utilised assessment tools approved by NICE (2012) for the diagnosis of ASD in an adult population and in both studies use of such tool depended on the availability of an informant (Mandell et al., 2012; Nylander & Gillberg, 2001). These studies estimated prevalence of ASD as 9.8% and 1.7% respectively and were thought to be associated with a medium level of risk of bias. Hallerback et al. (2012), who use a NICE-approved case identification instrument and then the DISCO-11 to interview informants where available, estimate prevalence at the higher rate of 27%. The remaining studies utilised case ascertainment methods that have not been recommended by NICE as constituting reliable means of identifying cases of ASD and report prevalence estimates ranging from 0.8% to 3.6% (Chang et al., 2003; Davidson et al., 2013; Fraser et al., 2012).

Based on these six included studies investigating occurrence of ASD in a psychosis population, it is difficult to arrive at a solid estimate of prevalence. Mandell et al.'s (2012) estimate of 9.8% is based on an inpatient psychiatric sample where complex, comorbid cases are likely to be more prevalent than in an outpatient clinic and therefore might be expected to constitute an overestimate. However, Hallerback and colleagues (2012) estimate significantly higher rates of prevalence (27%) in their sample, which they consider to be reasonably representative of all individuals with psychosis in the county of Värmland, Sweden. Given the small number of included studies, the relatively high risk of bias associated with the studies and their heterogeneity (particularly in terms of the specific ASD diagnoses included and the diagnostic criteria applied), meaningful comparison of reported figures is challenging. Effective assessment of ASD in adults involves gathering a range of information from multiple sources and NICE (2012) recommended structured assessment tools tend to be costly and time-consuming. As such, it is perhaps not surprising that studies estimating prevalence of ASD in a psychosis population are heterogenous and associated with considerable risk of bias. Nevertheless, in order for a meaningful prevalence range to be estimated, further studies are required benefitting from community samples, consistency in terms of the definition of ASD cases (e.g. ASD as defined by DSM-5; APA, 2013a) and utilising 'gold standard', NICE (2012) guideline approved adult assessment tools.

This review suggests that symptoms of psychosis may be more prevalent in individuals with ASD than in the general population. Research has sought to uncover factors which might explain such co-occurrence, including: (i) the possibility that the two disorders share the same aetiological underpinnings; (ii) the hypothesis that ASD is a separate disorder but constitutes a risk factor for developing

psychotic symptoms; and (iii) the possibility that, in a proportion of cases, there is no real co-occurrence of ASD and psychosis, rather the symptoms of ASD have been misconstrued as psychotic.

Whilst there are known risk factors contributing to each of ASD and psychotic disorders, how such factors fit together to cause each disorder has not been established and in many cases a complex interaction of genetic and environmental factors is likely to be involved (NICE, 2014; NICE, 2012). Environmental risks implicated in the aetiology of both ASD and psychotic disorders may include such factors as advanced parental age, maternal infection during pregnancy and low birth weight (DSM-5, APA 2013a; Cheung et al., 2010).

Genes are known to constitute a significant risk factor in both ASD and psychosis (NICE, 2012; NICE, 2014). However, in the majority of cases, such risk is thought to be polygenic, with multiple genetic loci making a small contribution (DSM-5; APA, 2013a; Sullivan, Kendler & Neale, 2003). Crespi et al. (2010), evaluating hypotheses explaining the genomic relationship between ASD and schizophrenia, found evidence to support partial overlap and diametric models of this relationship, but discounted the hypothesis that the two disorders are completely independent of one another, arguing that the overlap in genetic factors between them is greater than would be expected by chance. A diametric model of these two disorders was proposed by Crespi and Badcock (2008), who suggest that ASD and schizophrenia exist at either end of the same continuum of sociocognition. They argue that autism spectrum disorders reflect a bias towards the effects of paternally expressed genes, contributing to brain overgrowth and underdevelopment of social brain systems, manifesting in the theory of mind deficits characteristic of ASD. The underpinnings of psychotic disorders, on the other hand, are suggested to involve

biases towards the effects of maternally expressed genes, which mediate a general pattern of undergrowth and an overdevelopment of social brain systems, that is, a tendency to 'over-mentalise' (e.g. paranoia). A partial overlap model is evidenced (as discussed previously) by the presence of genomic risk factors common to both disorders, including duplications, deletions and particular alleles associated with ASD and schizophrenia (Crespi et al., 2010).

Both ASD and the psychotic disorders are associated with sociocognitive deficits, such as impaired theory of mind (Frith & Corcoran, 1996; Holroyd & Baron-Cohen, 1993; Sprong, Schothorst, Vos, Hox & Van Engeland, 2007). 'Theory of mind' or 'mentalising' is the ability to appreciate the existence of an individual's subjective state of mind (thoughts, beliefs, intentions) and to understand and predict behaviour on the basis of this appreciation. Studies have sought to uncover shared mechanisms underlying such social cognitive dysfunction in the two disorders. For example, Pinkham, Hopfinger, Pelphrey, Piven and Penn (2008), found significantly reduced neural activation of certain discrete brain regions involved in sociocognitive processing in an ASD group and a paranoid schizophrenia group as compared to a healthy comparison group whilst completing a task of complex social cognition. However, other studies have highlighted the heterogeneity in the neuroanatomical findings in the autism and schizophrenia literature (Sasson et al., 2011) and, over all, there has been a failure to show definitively why these areas of overlap occur.

An alternative possibility is that ASD and psychosis do not share overlapping aetiological processes but that ASD itself constitutes a risk factor for the development of psychotic symptoms in later life. NICE (2014) highlights psychological factors implicated in the development of psychotic symptoms, including problems with basic cognitive functions (such as learning, attention,

memory and planning) and biases in emotional and reasoning processes. ASD is known to be associated with deficits in these domains, for example, in executive functioning, central coherence, mindblindness and a lack of preferential attention to social stimuli contributing to difficulty reading emotions from face and voice (Frith & Happe, 2005). Such psychological characteristics commonly found in individuals with ASD may generate a particular vulnerability to developing symptoms of psychosis. The experience of growing up with a neurodevelopmental disorder such as ASD is also associated with broader psychosocial risk factors implicated in the development of psychotic symptoms, for example, childhood adversity including neglect and bullying (NICE, 2014).

A number of the studies reviewed here consider the possibility that symptoms of ASD have been misinterpreted as psychotic (e.g. Davidson et al., 2013; Raja & Azzoni, 2010). The overlap in symptomatology between the two disorders (e.g. socio-cognitive deficits, restricted interests, flattening of affect) has been noted. In addition, studies suggest that symptoms traditionally considered to be typical of psychotic disorders may also feature in ASD. For example, Raja and Azzoni (2010) suggest that hallucinations and delusions are inappropriately excluded from definitions of ASD and Dossetor (2007) highlights the presence of thought disorder in ASD and other conditions impacting language development. The diagnostic tools employed in the ascertainment of cases of autism spectrum and psychotic disorders may not be sophisticated enough to distinguish between the two conditions. Bastiaansen et al. (2011) reported limitations in the ability of module 4 of the ADOS to differentiate between individuals with ASD and those with schizophrenia characterised by negative symptoms. Nylander, Lugnegard and Hallerback (2008) suggest that the diagnosis of psychotic symptoms relies particularly heavily on an

individual's ability to communicate, which may hinder accurate diagnosis in individuals with the communication difficulties associated with ASD.

A number of limitations should be held in mind when considering the findings of this review. It was discovered that certain studies investigating the co-occurrence of ASD and psychosis did not include a term relating to 'psychosis' or 'schizophrenia' in their titles, abstracts or keywords, utilising instead the broader term 'psychopathology' to indicate an investigation into the occurrence of a range of psychiatric disorders in ASD. Whilst a number of such studies were discovered (for example, in the reference lists of included papers) it is possible that some relevant studies may have been missed due to the parameters of this particular systematic search. In addition, many of the studies included here provide prevalence estimates based on samples with mixed IQ scores making it difficult to distinguish between the impact of ASD and the impact of learning difficulty. It was not possible, due to restrictions of time and resource, to employ two researchers to evaluate papers identified by the search for relevance and to appraise the quality of the included studies independently, allowing for an assessment of interrater reliability of such judgements. As such, quality ratings reported in this review are subjective, and the reliability with which inclusion criteria were applied is untested. However, the ROBT was designed specifically for the assessment of prevalence studies and demonstrated good interrater reliability in Hoy and colleagues' findings (2012).

This review highlights a need for additional research in a number of areas. Well-designed epidemiological research, in particular large scale, population based, prospective studies, to provide a reliable estimate of co-occurrence of ASD and psychosis, is currently lacking. The validation of a measure designed specifically for the assessment of psychotic symptoms in an adult ASD population may also assist in

establishing the true prevalence of psychosis in this population. Given the heterogeneity of both autism spectrum and psychotic disorders, nosological considerations may also continue to need to be refined, to clarify which symptoms occur in both disorders and why. Improved detection of and/or distinction between ASD and psychosis is of vital importance. There is a need for valid and reliable ASD assessment tools that are capable of distinguishing between symptoms of ASD and those of other psychiatric disorders including psychosis. In particular, informant report measures for the assessment of ASD in adults would provide vital information as to the individual's childhood development and their functioning prior to onset of psychiatric symptoms. Such tools are likely to improve therapeutic strategies in the clinic and allow for targeted treatment of individuals, including those experiencing co-occurrence. This in turn will enable clinicians to improve the functioning and quality of life of individuals experiencing these disorders.

The reported findings have clinical implications. Clinicians working in ASD and psychosis services need to be mindful of the possibility of an association between these two disorders. On the one hand, care should be taken in the assessment process, to distinguish between subtle overlapping symptoms to avoid misdiagnosis. On the other hand, clinicians working in an ASD setting should consider the possibility that having ASD may constitute a risk factor for the development of psychotic symptoms and engage in watchful waiting and provide targeted support where appropriate. Psychosis services should consider the possibility that a diagnosis of ASD may have been missed in individuals presenting in the clinic. Where there is doubt as to an individual's symptomatology clinicians should aim to carry out a detailed assessment process which takes into account a

person's early childhood development. It is hoped that accurate diagnosis will allow for more effective treatment.

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PART 2: EMPIRICAL PAPER

The Developmental, Diagnostic and Dimensional Interview - Short Form Adult Version (3Di-sva): a tool for assessing autism spectrum disorders in adults – validation in a clinical population

Abstract

Background. There is a lack of validated tools for the assessment of autism spectrum disorder (ASD) in an adult population. Such tools need to function effectively in the face of complex clinical presentations seen in adult psychiatric services, that is, to unravel symptoms of ASD from those of comorbid mental health difficulties or from those of alternative psychiatric disorders with an overlapping symptom profile. The Dimensional, Developmental and Diagnostic Interview – short version for adults (3Di-sva) is a new, informant-report instrument consisting of 71 questions designed to gather a comprehensive history of an individual from early childhood to current functioning. The measure generates scores for subscales reflecting DSM-5 diagnostic criteria for ASD.

Aims. This study aimed to evaluate the psychometric properties of the 3Di-sva, including by assessing its ability to discriminate between adults with ASD and those diagnosed with other clinical disorders. The psychometric properties of an abbreviated version of the 3Di-sva algorithm, consisting of 49 questions focusing exclusively on the current functioning of the individual (3Di-sva current algorithm) were also examined.

Methods. The 3Di-sva was administered to a parent or other relative of 27 adults diagnosed with ASD and 20 clinical comparison adults with a range of mental health disorders. Where possible, estimated IQ data were collected from participants (ASD n=17, comparison n=17) and informant interviews were audio-recorded and independently coded to assess inter-rater reliability (ASD n=10, comparison n=19).

Results. This study found the full length 3Di-sva to be a reliable measure, demonstrating good interrater reliability and acceptable to good internal consistency. The full length 3Di-sva also showed good general criterion validity as assessed in the

context of this sample: ASD participants scored significantly higher than clinical comparison participants on all subscales of the measure, large effect sizes were found, and sensitivity (0.85) and specificity (0.90) were high. The 3Di-sva current algorithm was also found to have good interrater reliability and the majority of the subscales demonstrated good internal consistency. The current algorithm was found to have good criterion validity, with ASD participants scoring significantly higher than clinical comparison participants on all subscales. Sensitivity (0.85) and specificity (0.95) were found to be high.

Conclusions. This study provides promising evidence that the 3Di-sva is a well validated, reliable informant report instrument for the diagnosis of autism spectrum disorders in adults. It has been shown adequately to discriminate ASD from other mental health difficulties in an adult population. It is time-efficient and easy to administer. In future it will be important to examine the psychometric properties of the 3Di-sva when used in a more ecologically valid diagnostic setting, such as an adult ASD assessment clinic, where all individuals being assessed are suspected of having an autism spectrum disorder. Future research should also investigate the reliability and validity of the 3Di-sva with discrete clinical comparison groups of individuals diagnosed with specific mental health disorders, as well as assessing the psychometric properties of the current algorithm when used with informants who did not know the individual in childhood, for example, carers or friends.

Introduction

Autism spectrum disorders (ASD) are lifelong neurodevelopmental disorders characterised by (i) difficulties in social communication and interaction across a range of contexts, and (ii) restricted, repetitive behaviours and interests (Diagnostic and Statistical Manual of Mental Disorders, 5th ed.; *DSM-5*; American Psychiatric Association [APA], 2013a). Symptoms must manifest in early childhood, although these may not be recognised until later in life when social demands exceed an individual's abilities, and must cause functional impairment. Diagnosis is made on the basis of these behavioural criteria since no specific and reliable biological markers have been identified in ASD (Medical Research Council, 2001).

The conceptualisation of ASD has evolved considerably since Leo Kanner first published his observations of a group of children displaying marked difficulties with social interaction and repetitive behaviour in 1943. Historically, autism was widely regarded as a psychotic disorder (DSM-II, APA, 1968) and was attributed exclusively to environmental factors, such as, a cold parenting style (Bettleheim, 1967). In the 1970s, Michael Rutter's research (1978) identified certain key features of autism as a distinct disorder, symptoms present in virtually all children diagnosed with autism and rarely found in children without autism, namely severely impaired social skills, language delay and stereotyped behaviours or routines. Rutter (1978) also highlighted evidence for autism as a neurodevelopmental disorder, including physiological symptoms associated with autism, such as epilepsy, and the concordance of autism in identical twins. This was reflected in DSM-III (APA, 1980) which described a new class of disorder, the "pervasive developmental disorders", to which the diagnosis of "infantile autism" was assigned. DSM-III-R (APA, 1987) revised the definition of infantile autism to that of "autistic disorder"

and set out three key areas of impairment: (i) reciprocal social interaction; (ii) communication; and (iii) restricted interests.

Autism spectrum disorders continued to be conceptualised according to this triad of impairments until the publication of DSM-5 (APA, 2013a) when the separate dimensions of social interaction and communication were collapsed into a single category, reflecting research evidencing the construct validity of a dyadic model of ASD (e.g. Mandy, Charman & Skuse, 2012). In addition to introducing the autism dyad, DSM-5 replaced three separate autism sub-diagnoses set out in DSM-IV-TR (autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified; APA, 2000) with a single disorder: autism spectrum disorder. This reflected concerns about the reliability of these ASD subtypes, with research suggesting that they were not consistently distinguished from each other by clinicians (APA, 2013b). The current spectrum conceptualisation accounts for the variability in presentation of individuals with ASD by acknowledging that different presentations sit along a continuum from mild to very severe and that ASD can present with or without language and/or intellectual disability (APA, 2013b).

The spectrum construct is also consistent with challenges to the traditional concept of ASD as a categorically distinct disorder which manifests qualitatively differently from other clinical disorders and from a typically developing presentation (Constantino & Todd, 2003; Medical Research Council, 2001; Wing, 1988). There is evidence that the behavioural characteristics required for a diagnosis of ASD may in fact represent an extreme manifestation of traits which appear continuously in the general population (Posserud, Lundervold & Gillberg, 2006).

Estimates of the prevalence of ASD have also evolved since the 1970s when it was thought to be a fairly rare condition, present in only 4 per 10,000 children (Rutter, 1978). Contemporary childhood prevalence studies estimate occurrence to be approximately 1% of the population (Baird et al., 2006; Baron-Cohen et al., 2009) and suggest that for every three known cases of ASD there will be two undiagnosed individuals who may require assessment and support later in life (Baron-Cohen et al., 2009). This increase in the number of reported cases of ASD is thought to reflect greater public awareness, a broadening of diagnostic criteria and screenings for the disorder becoming more common (Chakrabarti & Fombonne, 2005). Prevalence of ASD in adulthood is estimated to be similar to that in children, at approximately 1.1% of the UK population (Brugha et al., 2012), contradicting any idea that people may 'grow out of' ASD and further countering the suggestion that ASD is becoming more prevalent. Studies of outcomes in adulthood confirm that individuals diagnosed with ASD in childhood remain disadvantaged in a range of domains, with few estimated as being able to function completely independently (e.g. Howlin & Moss, 2012).

Notwithstanding increased awareness of the condition, there is evidence that some individuals with ASD reach adulthood without ever receiving a diagnosis (Geurts & Jansen, 2011; Nylander & Gillberg, 2001). Ritvo, Ritvo, Freeman and Mason-Brothers (1994) suggest that individuals with mild or late-manifesting symptoms are less likely to present in the clinic until adolescence or adulthood and that these individuals present a particular diagnostic challenge to clinicians. ASD symptoms tend to fluctuate across the lifespan (Matson & Neal, 2009; Vannucchi et al., 2014), with important life events and transitions affecting the way in which symptoms present across the individual's development, yet the majority of

assessment tools were designed specifically with children in mind (National Institute for Health and Clinical Excellence [NICE], 2012). In addition, ASD shares significant overlap in symptomatology with other conditions, such as psychosis and mood disorders, which may lead to misdiagnosis (Rutter, 2013; Vannucchi et al., 2014). The diagnostic picture is further complicated by the fact that individuals with ASD are at increased risk of experiencing comorbid mental health difficulties, such as mood and anxiety disorders, (Geurts & Jansen, 2011; Skokauskas & Gallagher, 2010). ASD symptoms may be misattributed to such coexisting conditions.

Given the complexity associated with diagnosing ASD in adults, it is not surprising that studies have highlighted the struggle faced by adults in accessing a diagnosis (Taylor & Marrable, 2011). Adults with ASD are reported to suffer exclusion both socially and economically, with services often failing to identify the condition and provide appropriate support (NICE, 2012). In their review of follow-up studies on adults with ASD, Howlin and Moss (2012) concluded that adults with ASD are at increased risk of poor outcomes in terms of employment, social relationships, quality of life and physical and mental health. Diagnosis is vital in enabling individuals to receive much needed support from health and social services. However, charities such as The National Autistic Society describe adults struggling for years to obtain a diagnosis and even then finding that the diagnosis is challenged by services (The National Autistic Society, 2010). An understanding of the characteristics of the disorder, which may be facilitated by receipt of a diagnosis, can also help families and carers understand the individual's needs, behaviours and responses.

In recent years the UK government has recognised the need for improved diagnostic and care pathways for ASD. The Autism Act (2009) provided for

statutory guidance to be published setting out actions required by councils and health authorities to meet the needs of individuals with ASD in their local area. The resulting guidance (Department of Health, 2010) makes recommendations for the development of a clear and consistent pathway to diagnosis in every locality. The National Institute for Clinical Excellence endorses such a policy in its guideline for ASD in adults (NICE, 2012) which emphasises the need to capture patients through diagnosis and recommends the creation of specialist multi-agency teams to cater for this client group.

Effective assessment of ASD in adults involves obtaining a broad range of information from multiple sources in a diagnostic battery. It should include: enquiry as to the presence of core symptoms of ASD since childhood, a developmental history if possible, an assessment of the individual's functioning in a range of environments, such as home, education and employment, and understanding whether the individual may be hyper- or hypo-sensitive to sensory input (NICE, 2012). Such information is traditionally gathered by three means - self-report, direct observation and informant report – often with the aid of structured assessment tools (NICE, 2012).

Self-report tools provide valuable information as to the lived experience of the individual being assessed. The Ritvo Autism and Asperger Diagnostic Scale: Revised (RAADS-R; Ritvo et al., 2011) is a self-report tool recommended for use in the assessment of adults by NICE (2012) demonstrating good psychometric properties. It has been shown to have good internal consistency and test-retest reliability, as well as excellent sensitivity (97%) and specificity (100%), (Ritvo et al., 2011). However, concerns raised regarding the impact that psychological and cognitive deficits associated with ASD may have on an individual's insight into his

or her own symptoms (Bishop & Seltzer, 2012; Johnson, Filliter & Murphy, 2009) mean that self-report tools are rarely used in isolation.

Direct observation of the individual in situations designed to elicit behaviours relevant to a clinical diagnosis of ASD is a fundamental element of a comprehensive assessment process. The Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) is a widely used observational measure and has a module designed specifically for use with verbally fluent adults (module 4). It is the only observational tool recommended by NICE (2012) for use with adults. It is a well validated instrument, which has been shown to be reliable (Lord et al., 2000) and to demonstrate good sensitivity and adequate to good specificity (Hus & Lord, 2014). Concerns have been raised as to the ability of module 4 of the ADOS to distinguish between individuals with ASD and those with schizophrenia characterised by negative symptoms (Bastiaansen et al., 2011). Revisions to the module 4 algorithm in the ADOS-2 (Lord et al., 2012) were designed to achieve better differentiation between these groups, however further research is needed to confirm this (Hus & Lord, 2014). Extensive training is required before the ADOS can be administered and it is expensive to acquire, which may have resource implications in clinical settings (Charman & Gotham, 2013; NICE, 2012).

NICE (2012) recommends the involvement, where possible, of a family member or other informant in the assessment process in order to obtain information as to the individual's past and current behaviour and childhood development. However, adult-specific informant report measures for the assessment of ASD are currently lacking.

The Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter & Le Couteur, 1994) is a semi-structured interview originally designed for use with the parents of children with suspected ASD. It demonstrates good sensitivity and specificity (Lord et al., 1994) and has been assessed by NICE (2012) as having satisfactory reliability and validity data. Whilst NICE (2012) does recommend use of the ADI-R with adult populations, it highlights the fact that there are no data assessing the reliability or the construct and criterion validity of the ADI-R with adults. The ADI-R is also time-consuming to administer, taking up to three hours (Matson, Nebel-Schwalm & Mastson, 2007), and requires extensive and costly training prior to use.

The Diagnostic Interview for Social and Communication Disorders (DISCO; Wing, Leekham, Libby, Gould, & Larcombe, 2002) was also designed for use in the assessment of children and is distinctive in that it reflects a dimensional approach to the autism spectrum rather than focusing specifically on diagnostic categories set out in ICD (e.g. ICD-10; World Health Organisation, 1992) or DSM (e.g. DSM-IV-TR; APA, 2000). However, psychometric evidence as to use of the DISCO with adults is limited and therefore NICE (2012) does not recommend its use as a diagnostic tool in adult populations. In addition, as with the ADI-R, administration of the DISCO is a lengthy process (two to four hours; Charman & Gotham, 2013) which impacts on its utility in a clinical setting.

Two further informant report tools recommended by NICE (2012) are the Adult Asperger Assessment (AAA; Baron-Cohen, Wheelwright, Robinson, & Woodbury-Smith, 2005), and the Asperger Syndrome Diagnostic Interview (ASDI; Gillberg, Gillberg, Rastam & Wentz, 2001). The AAA, in recognition of the limitations of existing assessment instruments created for use with children, was

designed specifically for use with adults (Baron-Cohen et al., 2005) and the psychometric properties of the ASDI have been assessed in a population which includes adults (Gillberg et al., 2001). However, both these instruments were designed for the assessment of individuals with suspected Asperger Syndrome or High Functioning Autism and therefore do not measure the full range of ASD presentations described in DSM-5 (APA, 2013a). In addition, further research as to the validity and reliability of these instruments is needed. Currently only one published paper exists in respect of each instrument (Baron-Cohen et al., 2005; Gillberg et al., 2001) and these are authored by the original developer of the instrument and utilise relatively small sample sizes.

In view of the limitations in the quality of psychometric evidence for the use of existing informant report tools with adults and the practical constraints (such as, administration time, training and cost) associated with such tools, there is a need for a new ASD informant report measure to be designed and validated. Clinics with limited resources require an informant report measure which is user-friendly, time-efficient and easily accessible in terms of cost and training, as well as reliable and valid in adult populations.

The Dimensional, Developmental and Diagnostic Interview (3Di; Skuse et al., 2004) is a further standardised informant report measure, currently used in the assessment of ASD in children and adolescents. Whereas the ADI-R and the DISCO were designed primarily to assess individuals with below average IQ, the 3Di is capable of assessing autistic characteristics in children with either normal range abilities or with moderate or severe learning difficulties (Skuse et al., 2004). This approach reflects contemporary research suggesting that approximately half of individuals meeting criteria for ASD have an IQ in the normal range (Baird et al.,

2006). Responding to the evolution in the conceptualisation of ASD from a categorically distinct disorder to an extreme manifestation of traits which exist continuously in the general population, the 3Di was also devised to assess autistic characteristics dimensionally in both ASD and non-ASD populations (Skuse et al., 2004). Accordingly, the 3Di can indicate the presence of autistic traits in individuals who do not meet full diagnostic criteria for ASD, and was also devised to assess mental states relevant to potential comorbid diagnoses, potentially providing extremely useful information for tailored interventions (Skuse et al., 2004).

The 3Di originally consisted of 113 items, however a shorter version was later developed (3Di-sv; Santosh et al., 2009) which consists of just 53 items. The 3Di-sv has been shown to be valid and reliable for use with child populations (Santosh et al., 2009). As the age of participants in the study conducted by Santosh and colleagues ranged from 2.4 – 21.1 years (mean= 9.9, SD=3.3), this research raised the question of whether the instrument may also be suitable for use with adolescents and young adults.

The 3Di-sv was recently adapted to create a specific adult version of the interview (Dimensional, Developmental and Diagnostic Interview – Short Form Adult Version; 3Di-sva). Items for inclusion in the 3Di-sva were selected from the 3Di-sv based on their ability to discriminate between individuals with and without ASD in older adolescents. Certain of these items were then amended to ensure the question made sense when applied to an adult, for example, when asking a question about childhood behaviour, clarifying that this took place in the past:

"When [name] was at primary school, did he ask if he could invite friends over?" New items were also added to reflect specific features of the ASD phenotype in adults, based on expert clinical opinion, for example:

"Have there been times when [name] has been easily led by others, resulting in (him/her) getting into trouble?"

More recently, items have been added to reflect the new diagnostic criteria for ASD set out in DSM-5 (APA, 2013a), including the emphasis on unusual sensory responses:

"Is (he/she) ever distressed by everyday sounds, such as, the noise of a vacuum cleaner, food processor or hand dryer?".

The 3Di-sva includes 71 questions aimed at gathering a comprehensive history ranging from early childhood development to current functioning. The interview can be completed in 45 minutes and individuals can be trained in its administration in around an hour. Scoring can be carried out using a computer algorithm.

A pilot study to validate the 3Di-sva in ASD and typically developing adult populations has been carried out. These initial data are promising, showing that the 3Di-sva is able to discriminate effectively between typically developing adults and adults with an ASD. However, further research is required to provide a more detailed assessment of the validity and utility of the tool. The pilot study investigated the psychometric properties of an older version of 3Di-sva designed to reflect the triadic characterisation of ASD set out in DSM-IV-TR (APA, 2000). The 3Di-sva algorithm has since been updated to reflect the reconceptualisation of ASD as a dyad of impairments in DSM-5 (APA, 2013a). In addition, given the high prevalence of comorbid mood and anxiety disorders in individuals with ASD (Geurts

& Jansen, 2011) and the significant overlap in symptomatology between ASD and schizophrenia (Bastiaansen et al., 2011; Sprong, Schothorst, Vos, Hox & Van Engeland, 2007), it is important to assess the ability of the 3Di-sva to discriminate accurately between adults with ASD and adults with other psychiatric presentations. This represents a more difficult and ecologically relevant test of the measure's criterion validity.

The current study aims to analyse the psychometric properties of the 3Di-sva by examining the reliability, criterion validity, and sensitivity and specificity of the measure. Criterion validity of the measure will be assessed by examining its ability to discriminate between individuals diagnosed with ASD and individuals without ASD who have been diagnosed with other clinical disorders. A concurrent study (Clarke, 2015), completed jointly with this project, investigated the ability of the 3Di-sva to discriminate between individuals with ASD and those with no clinical history.

Given that adults presenting with suspected ASD do not always have easy access to an informant who knew them well in childhood, this study also aims to assess the psychometric properties of an alternative scoring algorithm for the 3Di-sva, which only takes into consideration questions about the individual's behaviour currently and excludes questions about childhood (3Di-sva current algorithm). The reliability, criterion validity, and sensitivity and specificity of the 3Di-sva current algorithm will be assessed.

Research questions

1. Is the 3Di-sva a reliable measure, as demonstrated by good:

(i) interrater reliability, and

(ii) internal consistency?

2. Does the 3Di-sva have criterion validity, as demonstrated by its ability to discriminate effectively between adults with ASD and adults with other clinical disorders on each of the two dimensions of ASD identified by DSM-5 (APA, 2013a), (i) social communication and interaction, and (ii) restricted, repetitive patterns of behaviour, interests or activities?

3. What is the optimal cut-off threshold for the 3Di-sva in distinguishing between ASD cases and non-ASD cases in a psychiatric population, maximising sensitivity and specificity of the measure?

4. In respect of the 3Di-sva current algorithm:

(i) does the 3Di-sva current algorithm demonstrate good interrater reliability and internal consistency?

(ii) does the 3Di-sva current algorithm discriminate effectively between adults with ASD and adults without ASD but with other clinical disorders?

(iii) what is the optimal cut-off threshold for the 3Di-sva current algorithm in distinguishing between ASD cases and non-ASD cases in a psychiatric population, maximising sensitivity and specificity of the measure?

Method

Design

A cross-sectional, between subjects design was used to assess the psychometric properties of the 3Di-sva when used with individuals with ASD and individuals with other mental health difficulties.

Joint thesis

This thesis formed part of a joint research project and was completed with fellow UCL trainee clinical psychologist, Kiri Clarke (Clarke, 2015). See Appendix C for further details of individual contributions to the research.

Participants

Sample

Three samples were recruited between August 2014 and June 2015 for the joint research project with Clarke (2015): a group of individuals diagnosed with ASD (ASD group), a group of individuals without ASD but diagnosed with other mental health difficulties (clinical comparison group) and a group of individuals without ASD or other mental health difficulties (non-clinical comparison group). Analyses in respect of the non-clinical comparison group were carried out by Clarke (2015). Analyses in respect of the ASD and clinical comparison groups were conducted in this study.

Inclusion and exclusion criteria

All participants were required to: 1) be aged 18 or over, 2) have a reported estimated IQ of 70 or above, that is, in the "average" range (where IQ data were not obtained, IQ was assumed to be in the "average" range), and 3) have a parent or other informant willing to complete the 3Di-sva.

Additional inclusion criteria for the ASD group were: 1) the individual was assessed by means of an ADOS, module 4, and achieved the cut-off scores for autism spectrum classification, and 2) a diagnosis of ASD was reached by clinical consensus on the basis of all available data, applying DSM-IV-TR criteria for autistic disorder or Asperger's disorder, or DSM-5 criteria for autism spectrum disorder. Meeting ADOS assessment criteria for ASD was considered a prerequisite for inclusion in the

ASD group to ensure that the diagnosis had been established by means of a 'gold standard' ASD assessment tool. Formal diagnosis of ASD was then confirmed by the clinical team on the basis of all elements of a comprehensive assessment process (NICE, 2012) and to protect against the possibility of false positive diagnoses pursuant to the ADOS.

Individuals were included in the clinical comparison group if they had received a clinical diagnosis of a mental health disorder. In fifteen cases formal diagnoses were reported directly to the researchers by the appropriate NHS team. In four cases diagnoses were reported by the participants themselves and it was not possible to verify the information with the clinicians who provided such diagnoses. In the case of one participant recruited via the IAPT service, the exact diagnosis was unknown, although it was known that the individual had received cognitive behavioural therapy at the service. Participants were excluded from the clinical comparison group if: 1) there were any concerns that the individual may have ASD and such concerns had not been excluded following a clinical assessment, 2) the researcher collecting informed consent assessed the individual as lacking mental capacity to consent, 3) the participant or participant's parent had insufficient English language fluency to be able to understand the relevant measures and interview questions (due to there being insufficient resources to provide an interpreter). Individuals recruited from the IAPT service were excluded if their only diagnosis at the time was one of Post-Traumatic Stress Disorder, as another research project was recruiting such participants at the time.

Sample characteristics

The ASD group consisted of 27 participants aged 18-59 and the clinical comparison group of 20 participants aged 21-50. Individuals in the clinical comparison group had received a range of mental health disorder diagnoses: mixed anxiety and depression (*n*=7), depression (*n*=4), anxiety (*n*=4), borderline personality disorder (*n*=2), psychotic disorder (*n*=1), anger and interpersonal difficulties (*n*=1). The diagnosis of one individual attending a step 3 IAPT service was unknown. Characteristics of the ASD and clinical comparison groups are presented in Table 1.

The aim was to recruit a minimum of 20 participants (and a parent or other informant in each case) to each group. This figure was based on similar numbers recruited in studies attempting to validate comparable measures (e.g. Bastiaansen et al., 2011; Lord et al., 1994) and on practical limitations, such as time and resources. Numbers in this study were not based on a power analysis since differences between the groups were expected to be large and the study was not concerned with the 3Di-sva's capacity to detect small, subtle between-group differences.

Table 1
Characteristics of the sample

	Whole sample	**ASD group**	**Clinical comparison group**	**Significance of group difference**
	N=47*	n=27*	n=20*	
Number of males (%)	24 (51.1%)	18 (66.7%)	6 (30.0%)	$X^2(1) = 6.18$, $p = .01$
Mean age in years (SD) **Range**	33.83 (12.10) 18-59	35.63 (13.32) 18-59	31.26 (9.90) 21-50	$U = 221.50$, $z = -.78$, $p = .43$
Estimated IQ‡ (SD) **Range**	108.55 (14.85) 72-138	109.47 (16.89) 72-138	107.64 (12.96) 88-134	$t(32)=0.36$, $p=.73$
Years of education (SD) **Range**	17.15 (2.74) 11-25	17.60 (2.01) 14-20	16.88 (3.12) 11-25	$t(25)=0.65$, $p=.52$

Note: * Due to missing data: *N* ranges from 27-47 for the whole sample and *n* ranges from 10-27 for the ASD group and from 17-20 for the clinical comparison group.
‡ Estimated IQ data were obtained for 17 ASD participants and 17 clinical comparison participants. IQ is based on TOPF scores in all but eight of these cases; two ASD participants were assessed using the WASI and six ASD participants were assessed using the WAIS-IV.

Recruitment Procedure

Participants in the ASD group were recruited from two adult ASD assessment clinics in London (see Figure 1).

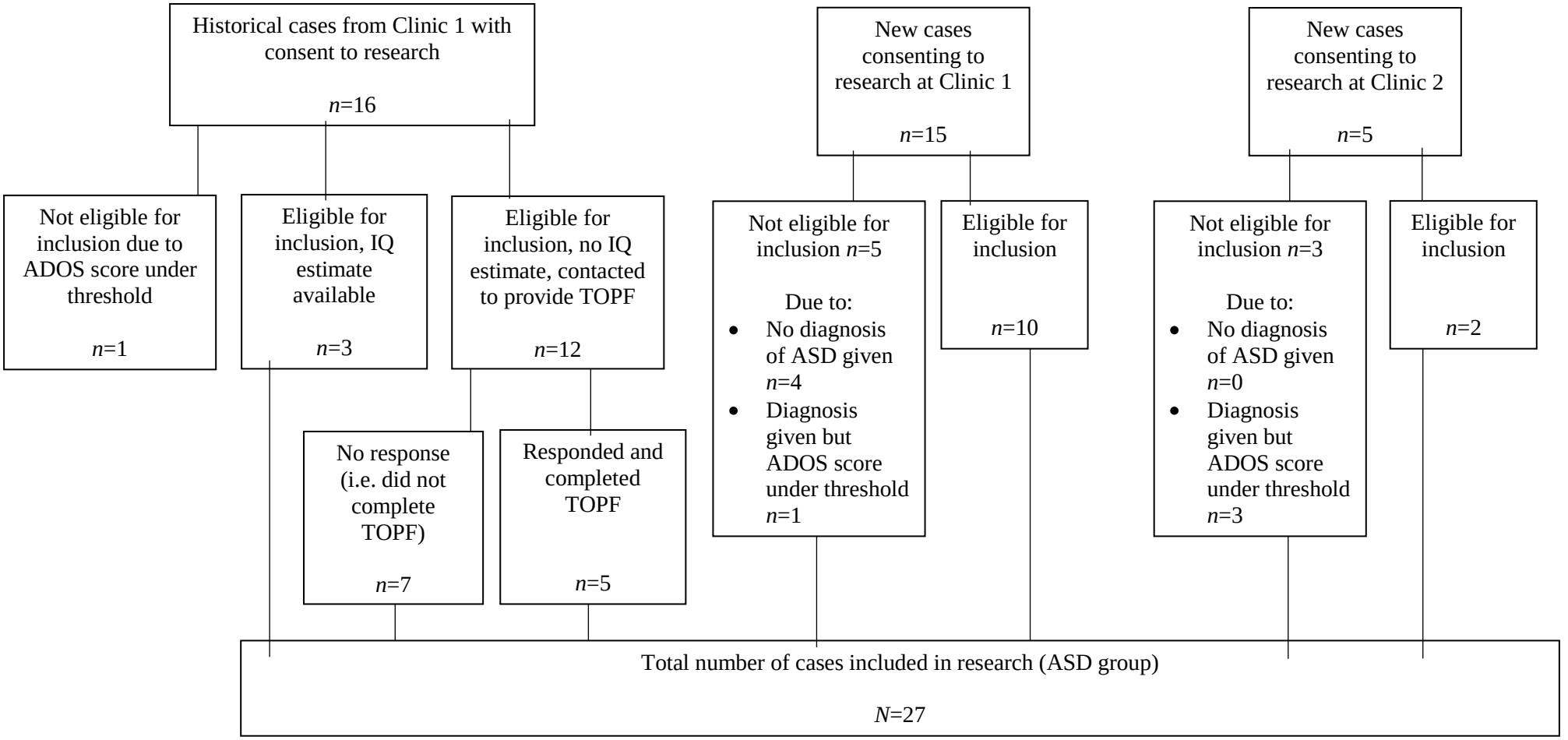

Figure 1. ASD group recruitment flowchart.

Both services conduct a clinical interview and administer a battery of tests as part of the assessment procedure, including the ADOS module 4, an assessment of IQ and, where there is an informant available, the 3Di-sva as a means of obtaining richer data as to an individual's developmental history and current presentation across a range of contexts. Decisions around diagnosis are reached by consensus of the multidisciplinary team of clinical psychologists and consultant psychiatrists. Twelve participants were recruited in the clinic at the time of their ASD assessment. Fifteen participants who had received their ASD diagnosis prior to commencement of this study (ASD research database participants) had consented at the time to the use of anonymised data for the purpose of research. Where there were no IQ data on record for the ASD research database participants, they were approached by a researcher and asked to complete the Test of Premorbid Functioning (TOPF; Wechsler, 2009).

Participants in the clinical comparison group were recruited from a number of sources: 1) individuals with severe and enduring mental health difficulties were recruited from secondary care community mental health services in London, 2) individuals clinically assessed as having an affective disorder were recruited from an IAPT service in London, 3) opportunistic recruitment of individuals currently receiving treatment for mental health difficulties who contacted the researchers after hearing about the study, and 4) individuals assessed by one of the ASD assessment clinics referred to above, where an ASD diagnosis was excluded and a diagnosis of other mental health difficulties was given. Of the four individuals recruited from secondary care services, two were approached by a researcher directly in the clinic waiting room and two were notified of the research project by a clinician involved in the individual's care. The participants recruited from IAPT services were on a database of individuals consenting to be contacted in relation to research projects.

The researchers wrote to individuals on this database, inviting them to participate in the project. Eight participants responded and completed their participation. Four individuals were recruited to the study from the ASD clinic at the time of their assessment there. These participants were allocated to the clinical comparison group following a clinical consensus as to a diagnosis of mental health disorder rather than an ASD diagnosis best explaining their difficulties. The remaining four participants, were recruited opportunistically to the clinical comparison group after hearing about the project directly from the researchers or from friends of the researchers.

Ethics

Ethical approval for this study was granted by the Bloomsbury NRES Committee (Ref 14/LO/1134) and by the Research and Development departments of NHS trusts in which participants were recruited (Appendix D). Prior to taking part, individuals (other than ASD research database participants) were given an electronic or hard copy of the information sheet setting out details of the study (Appendix E). All individuals were asked to provide written, informed consent prior to participating (see Appendix F). In the case of ASD research database participants, consent to the use of anonymised data in research projects was obtained at the time they attended the clinic for their ASD assessment. All personal data collected in connection with this project was stored and utilised in accordance with the Data Protection Act 1988. See Appendix G for invitation letter sent to ASD research database participants and Appendix H for invitation letter sent to individuals on the IAPT database.

Measures

Developmental, Diagnostic and Dimensional Interview (Short Form Adult Version) (3Di-sva) (Appendix I)

The 3Di-sva is a semi-structured interview for the assessment and diagnosis of autism spectrum disorders in adults. The interview is designed to be conducted with a parent of the individual being assessed, or with another informant who has known the individual well since childhood. It asks questions about early childhood development as well as current behaviour, providing a dimensional assessment of the areas of autistic impairment highlighted by DSM-5 (APA, 2013a).

The 3Di-sva interview consists of 71 questions. Sixty seven of these questions contribute to the full length scoring algorithm, whilst the remaining four questions relate to developmental milestones. Forty nine of the 67 questions constituting the full length scoring algorithm relate to the individual's behaviour as an adult, whereas eighteen questions relate to behaviours manifesting in childhood and rely on the informant having fairly detailed knowledge of the individual growing up. Algorithm questions contribute to one of two scales, reflecting the two key domains of symptomatology associated with ASD as cited in DSM-5 (APA, 2013a): the "A scale" assesses the individual's social interaction and communication skills and the "B scale" assesses restricted, repetitive patterns of behaviour, activities or interests. Within the A and B scales are 3 and 4 subscales (respectively), reflecting the criteria set out in DSM-5. The full length 3Di-sva scales and subscales are displayed in Figure 2.

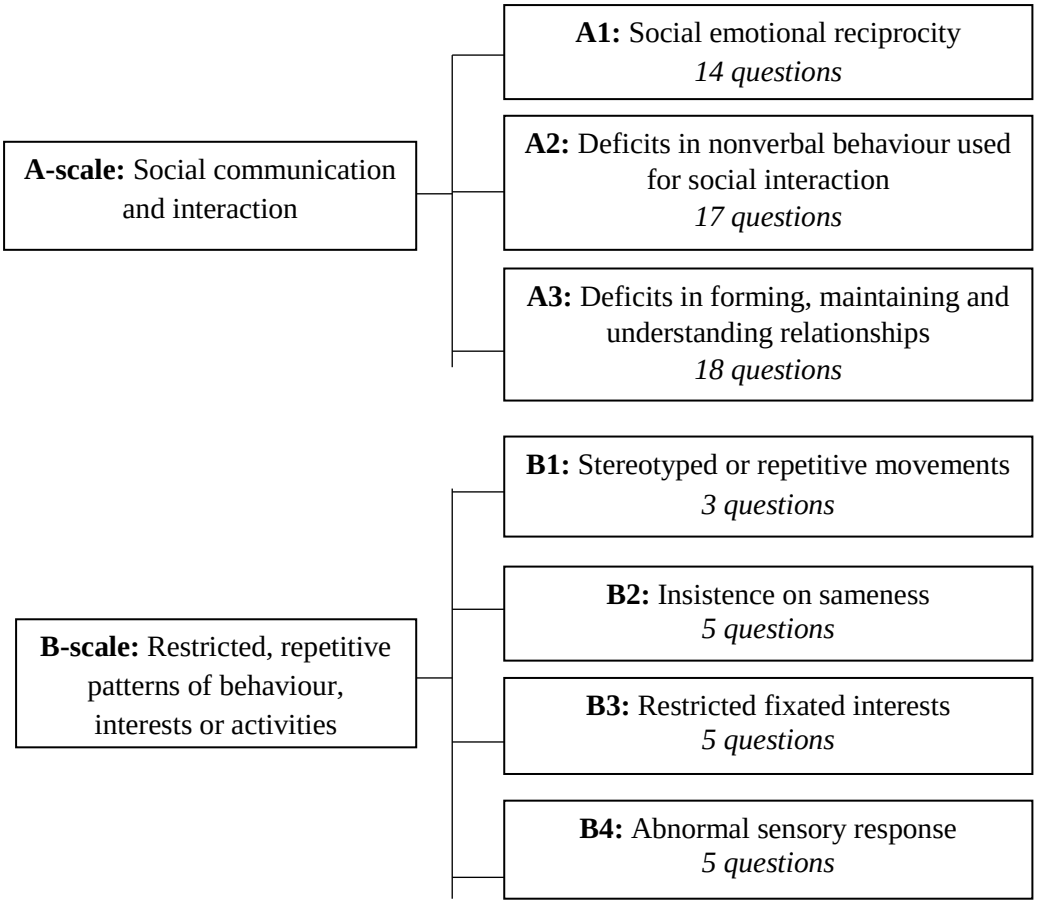

Figure 2. 3Di-sva full length scoring algorithm.

Questions contributing to the scoring algorithm are scored on a three or four point Likert scale (from 0 to 2 or 0 to 3) with higher scores indicating greater impairment. The remaining questions, relating to developmental milestones, are scored as either within, or outside of, the normal range. To ensure that all items within a scale carry equal weight, responses scoring 3 are recoded to a score of 2. Total scores for each of the seven subscales are calculated by summing the scores for all applicable questions and then dividing by the total number of questions to create a scaled score for each subscale of between 0 and 2. Overall scores for the A-scale (Social Communication) and the B-scale (Restricted repetitive behaviour, interests or activities) are then generated. As can be seen in Figure 2, a much greater number of questions contributes to the A scale subscales than the B scale subscales. Scaling the

subscale scores as explained above ensures that each subscale carries equal weight. See Appendix J for a complete copy of the full length scoring algorithm.

3Di-sva - current algorithm

An alternative scoring algorithm was developed for the purposes of this study, called the 3Di-sva current algorithm. Only the 49 questions relating the individual's current, as opposed to childhood, behaviour contribute to this 3Di-sva current algorithm, whereas scores for the 18 3Di-sva questions which relate to the individual's childhood development and childhood behaviours are excluded. The structure of the 3Di-sva current algorithm is displayed in Figure 3. As with the algorithm for the complete 3Di-sva, scores contribute to the A and B scales and subscales within them. See Appendix K for a complete copy of the current scoring algorithm.

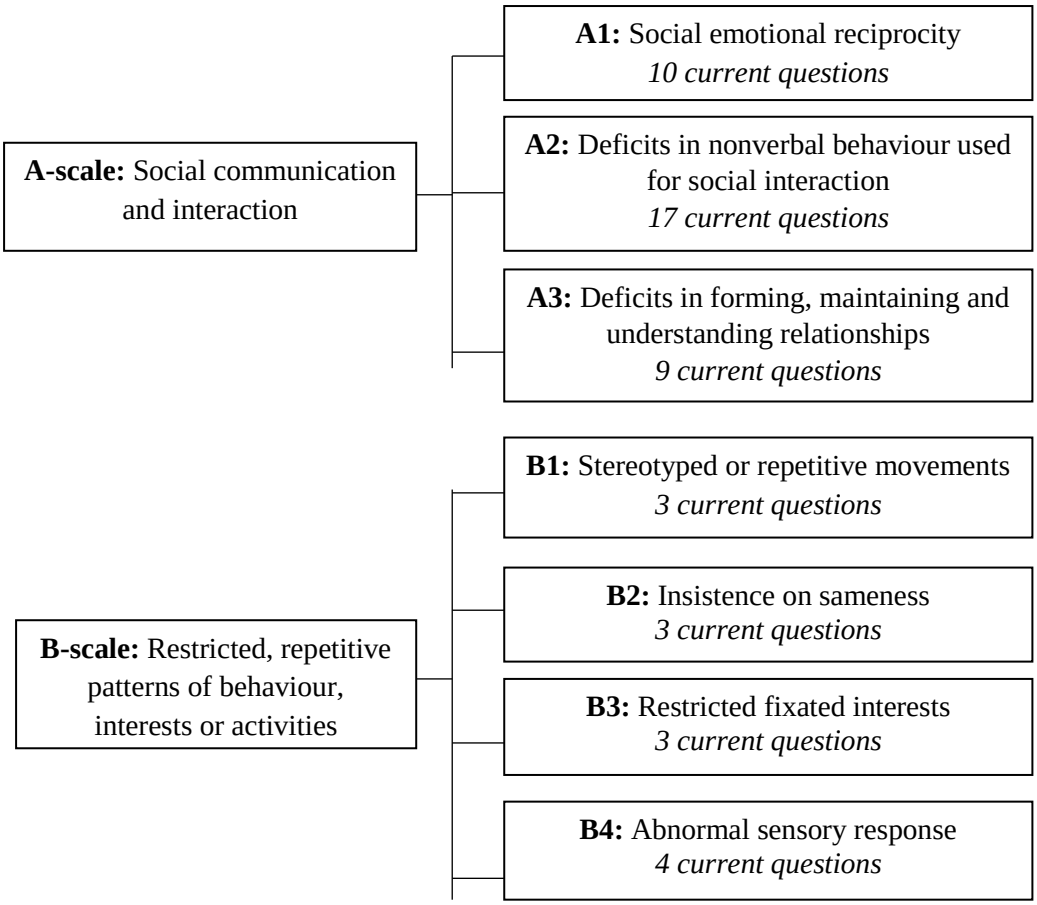

Figure 3. 3Di-sva current scoring algorithm.

Autism Diagnostic Observation Schedule (ADOS-G) Module 4 (Lord et al., 2000) and ADOS Diagnostic Observation Schedule 2 (ADOS-2) Module 4 (Lord et al., 2012)

The ADOS is a standardised semi-structured assessment tool used in the diagnosis of ASD. It consists of questions and activities designed to elicit behaviours associated with ASD, assessing language and communication, reciprocal social interaction, imagination and stereotyped behaviours and restricted interests. Module 4 of the ADOS was designed for use with verbally fluent older adolescents and adults. It focuses less on play activities (as with modules designed for younger children) and more on conversation with the individual being assessed. Module 4

takes around 45-60 minutes to administer. In this study two different versions of the ADOS were used: the ADOS-G (in 11 cases) and the more recent ADOS-2 (in 17 cases). Scoring algorithms in the two versions of the ADOS are directly comparable.

On the basis of observations made and notes taken during administration of the ADOS, behaviours are rated on a 0-2 or 0-3 scale, with higher scores indicating greater symptom severity. These ratings are converted to algorithm scores to calculate overall scores for the domains of (i) communication and (ii) social interaction. Each of these domain scores, as well as the combination of those two scores, must meet or exceed a predetermined cut-off in order for a diagnosis of ASD to be considered. Imagination/creativity and stereotyped behaviours and restricted interests scores are also generated but these do not count towards the diagnostic algorithm. These data can then be used in conjunction with other available information as part of a gold-standard ASD assessment. The ADOS is a well validated instrument with good psychometric properties (Charman & Gotham, 2013; Lord et al., 2000).

Test of Premorbid Functioning – UK version (TOPF; Wechsler, 2009)

The TOPF is a brief measure of full scale IQ for individuals aged 16 to 89 years. The test involves reading out loud a list of up to 70 words that have atypical grapheme to phoneme translations. If the individual pronounces five consecutive words incorrectly the test is stopped at that point. The TOPF takes around 5-10 minutes to complete. The individual's full scale IQ score is predicted based on the number of words pronounced correctly, the number of years spent in education and the individual's age. The TOPF provides an estimate of pre-morbid intellectual ability and is designed not to be affected by symptoms of mental health disorders, such as lack of motivation, which might impact performance. The TOPF has been

shown to be a reliable measure: it was found to have a high level of internal consistency (0.95) in the UK standardisation sample and to demonstrate good test-retest reliability (0.89-0.95) in the US standardisation sample (Wechsler, 2009). The TOPF also performs well when predicting full scale IQ as estimated by the Wechsler Adult Intelligence Scale-fourth edition (WAIS-IV; Wechsler, 2008), particularly when used in combination with demographic variables (correlation of 0.81 in the UK standardisation sample). The TOPF has been validated for use in a range of populations including individuals with ASD.

Procedures

3Di-sva interviews

All interviewers conducting the 3Di-sva in this study had been trained in its use. Interviews for the clinical comparison group were conducted by the researchers. Interviews for the ASD group were carried out by a researcher (n=10) or, in the case of all historic ASD research database participants as well as two newly recruited participants, by a clinician at the ASD clinic where the individual was being assessed (n=17). The majority of interviews in respect of clinical comparison participants were conducted over the telephone (n=17); the remaining three interviews were carried out in person, at the mental health or ASD clinic where the participant had been recruited. Interviews in respect of newly recruited ASD participants were carried out in person at the ASD clinic (n=7) or over the telephone (n=5). The method of administration in respect of ASD research database participants is uncertain, although clinicians reported that the majority were administered in person.

Interrater reliability

An undergraduate psychology student, trained in the 3Di-sva, was recruited as a research assistant to assist with the assessment of interrater reliability. Interviews were audio-recorded by the researchers where possible (ASD group n=10, clinical comparison group n=19) and these recordings were provided to the research assistant for the purposes of independent scoring. The research assistant was blind as to which group the recording related to.

Assessment of cognitive abilities

Attempts were made to obtain estimated IQ data in respect of all participants so that the groups could be compared in terms of IQ levels. Where IQ data had not already been obtained as part of their clinical assessment, participants in the ASD group were asked to complete a TOPF with one of the researchers (n=9). Existing IQ assessment data were used in respect of eight individuals in the ASD group. Assessment tools used in these cases were the WASI (Wechsler, 1999; n=2) and the WAIS-IV (Wechsler, 2008; n=6). TOPF data were collected from participants in the clinical comparison group where possible (n=17).

Assessment of ASD

All individuals in the ASD group were assessed for ASD using module 4 of the ADOS. Four participants in the clinical comparison group were also assessed for ASD using the ADOS but were found not to have ASD and were given other mental health diagnoses.

Thanking participants for their time

Participants and informants in the clinical comparison group were each given a £10 voucher to thank them for their time. It was decided not to offer participants in the ASD group vouchers because their data were collected as part of the routine

clinical assessment and it was thought to be unethical to pay some individuals attending the clinic when others would not be offered this opportunity.

Analyses

Statistical Package for Social Sciences (SPSS Version 22) was used to perform all analyses.

Preliminary analyses. Variables were screened to assess for normality of distribution. Differences between the two groups on age, gender, estimated IQ and years of education were also analysed.

Internal consistency. For each of the scales and subscales of the 3Di-sva, Cronbach's alpha was calculated.

Interrater reliability. Interrater reliability of the interview scores on each of the 3Di-sva scales and subscales was assessed using intraclass correlation coefficients (ICCs).

Criterion validity. The ability of the 3Di-sva to discriminate between the ASD group and the clinical comparison group was assessed using Mann Whitney *U* tests. The tests were used to detect statistically significant differences between the groups on A scale (social communication and interaction**)** and B scale (restricted repetitive patterns of behaviour, interests or activities) scores, as well as on each of the subscales. Where there were missing data, subscale scores were prorated using the mean item score, provided no more than 50% of the data were missing.

Sensitivity and specificity. Receiver operating characteristic (ROC) analysis was used to establish optimal cut-offs for the 3Di-sva in distinguishing ASD cases from

non-ASD cases in a psychiatric population, maximising sensitivity and specificity of the measure.

3Di-sva current algorithm. 3Di-sva scale and subscale scores were re-calculated for all participants using the 3Di-sva Current Algorithm and the analyses outlined above were conducted in respect of these scores.

Results

Preliminary Analyses

Normality of distribution

For each group of participants, variables of age, estimated IQ and years of education were screened to assess for normality of distribution. Variables were examined visually and the Kolmogorov-Smirnov test of normality was carried out in each case. Distribution of age varied significantly from normality in both the ASD ($D(27)=.17$, $p=.04$) and the clinical comparison groups ($D(20)=.17$, $p=.04$). Distribution of estimated IQ and years of education was normal in both groups.

The distribution of 3Di-sva full algorithm scales and subscales was also examined by means of visual examination and the Kolmogorov-Smirnov test. Kolmogorov-Smirnov test results are presented in Table 2. All scales in the clinical comparison group and in the combined group were found to deviate significantly from normality; distributions were positively skewed due to a greater proportion of scores falling at the bottom end of the scale. In the ASD group all scales were distributed normally, other than subscale B2.

Table 2
Kolmogorov-Smirnov test for normality of distribution of 3Di-sva variables

3Di-sva scale / subscale	ASD group	Clinical comparison group	Whole sample
A scale	$D(27)=.09$, $p=.20$	$D(20)=.33$, $p<.001$***	$D(47)=.17$, $p=.001$**
A1	$D(27)=.10$, $p=.20$	$D(20)=.26$, $p=.001$**	$D(47)=.16$, $p=.006$**
A2	$D(27)=.16$, $p=.094$	$D(20)=.31$, $p<.001$***	$D(47)=.13$, $p=.046$*
A3	$D(27)=.13$, $p=.20$	$D(20)=.30$, $p<.001$***	$D(47)=.15$, $p=.007$**
B scale	$D(27)=.08$, $p=.20$	$D(20)=.23$, $p=.008$**	$D(47)=.14$, $p=.021$*
B1	$D(26)=.13$, $p=.20$	$D(20)=.49$, $p<.001$***	$D(46)=.26$, $p<.001$***
B2	$D(27)=.23$, $p=.001$**	$D(20)=.38$, $p<.001$***	$D(47)=.19$, $p<.001$***
B3	$D(27)=.12$, $p=.20$	$D(20)=.26$, $p=.002$**	$D(47)=.15$, $p=.011$*
B4	$D(27)=.13$, $p=.20$	$D(20)=.36$, $p<.001$***	$D(47)=.19$, $p<.001$***

* deviation from normality significant at $p<.05$ level
** deviation from normality significant at $p<.01$ level
*** deviation from normality significant at $p<.001$ level

Analyses in respect of non-normally distributed variables were carried out by means of non-parametric statistical tests.

Differences between the groups

Differences between the ASD and clinical comparison groups on age, gender, estimated IQ and years of education were also analysed. There were no significant differences between the two groups in terms of age ($U = 221.50$, $z = -.78$, $p = .43$), estimated IQ ($t(32)=0.36$, $p=.73$) or years of participant education ($t(25)=0.65$, $p=.52$). However, there was a significant difference in the proportion of males in each group ($X^2(1) = 6.18$, $p = .01$), with 67% of participants in the ASD group being male compared to 30% of participants in the clinical comparison group.

Analyses in respect of the 3Di-sva full algorithm

Internal consistency

Cronbach's alpha correlation coefficients were computed for each of the scales and subscales of the 3Di-sva full algorithm (Table 3). All scales were found to be in the good to excellent range, excluding subscale B1 ($\alpha = 0.67$; stereotyped repetitive movements or speech) which fell slightly below the minimum recommended Cronbach's alpha coefficient of 0.7 (Kline, 2000). Cronbach's alpha for each item of the scales was also examined to assess whether deletion of an item would significantly improve Cronbach's alpha coefficient for the relevant scale. As the deletion of an item did not improve Cronbach's alpha by more than 0.02, no specific item was considered to impact sufficiently upon a scale's Cronbach's alpha to justify its deletion.

Interrater reliability

Intraclass correlations were high, with each of the 3Di-sva full algorithm scales and subscales yielding ICCs in excess of 0.9 (Table 3).

Table 3

Internal consistency and interrater reliability of each scale and subscale of the 3Di-sva, full algorithm

3Di-sva full algorithm scale / subscale	Internal consistency (Cronbach's α)	Interrater reliability (ICC)
	N=47‡	**N=28†**
Social communication and interaction ('scale A')	0.97	0.99*
Social emotional reciprocity (subscale A1)	0.86	0.99*
Deficits in non-verbal behaviour used for social interaction (subscale A2)	0.91	0.98*
Deficits in forming, maintaining and understanding relationships (subscale A3)	0.94	0.98*
Repetitive interests ('scale B')	0.93	0.99*
Stereotyped repetitive movements or speech (subscale B1)	0.67	0.97*
Insistence on sameness (subscale B2)	0.86	0.98*
Restricted fixated interests (subscale B3)	0.79	0.96*
Abnormal sensory response (subscale B4)	0.80	0.93*

Note: ‡ Due to missing data: *N* ranges from 21-45 for internal consistency analysis.
† A sample of 29 participant 3Di-sva interviews were assessed for interrater reliability. Due to missing data *N* ranges from 27-28 for this analysis.
* $p < 0.001$

Criterion validity

Mean scores obtained by the ASD group and the clinical comparison group on each 3Di-sva full algorithm scale and subscale are displayed in Table 4. Mann Whitney *U* tests show that the ASD group scored significantly higher than the clinical comparison group on all nine of the scales. All effect sizes are above the r=.5 threshold for a large effect (Field, 2005).

Table 4
Differences in 3Di-sva full algorithm scores between groups (N=47)

Scale / subscale of the 3Di-sva full algorithm	Range‡	ASD n=27†	Clinical comparison group n=20	Significance	Effect size
Social communication and interaction (scale A)	0-6				
Mean (SD)		3.07 (0.74)	0.74 (0.97)	U = 33.00, z = -5.10, $\mathbf{p < .001}$	r = -0.74
Median		3.04	0.26		
Social emotional reciprocity (A1)	0-2				
Mean (SD)		1.07 (0.27)	0.26 (0.39)	U = 45.00, z = -4.86, $\mathbf{p < .001}$	r = -0.71
Median		1.08	0.12		
Deficits in non-verbal behaviour used for social interaction (A2)	0-2				
Mean (SD)		0.92 (0.41)	0.18 (0.28)	U = 36.00, z = -5.07, $\mathbf{p < .001}$	r = -0.74
Median		0.80	0.00		
Deficits in forming, maintaining and understanding relationships (A3)	0-2				
Mean (SD)		1.08 (0.29)	0.30 (0.34)	U = 28.00, z = -5.21, $\mathbf{p < .001}$	r = -0.76
Median		1.00	0.17		
Repetitive interests (Scale B)	0-8				
Mean (SD)		4.06 (2.12)	0.65 (0.79)	U = 35.50, z = -5.06, $\mathbf{p < .001}$	r = -0.74
Median		4.33	0.37		
Stereotyped repetitive movements or speech (B1)	0-2				
Mean (SD)		0.91 (0.63)	0.08 (0.24)	U = 60.00, z = -4.67, $\mathbf{p < .001}$	r = -0.69
Median		1.00	0.00		

Scale / subscale of the 3Di-sva full algorithm	Range‡	ASD n=27†	Clinical comparison group n=20	Significance	Effect size
Insistence on sameness (B2)	0-2				
Mean (SD)		1.30 (0.58)	0.22 (0.36)	U = 43.00, z = -4.98, $\mathbf{p < .001}$	r = -0.73
Median		1.40	0.00		
Restricted fixated interests (B3)	0-2				
Mean (SD)		1.08 (0.63)	0.20 (0.30)	U = 53.50, z = -4.71, $\mathbf{p < .001}$	r = -0.69
Median		1.00	0.10		
Abnormal sensory response (B4)	0-2				
Mean (SD)		0.79 (0.65)	0.15 (0.21)	U = 111.50, z = -3.51, $\mathbf{p < .001}$	r = -0.51
Median		0.80	0.00		

‡ Higher score signifies greater impairment
† Due to missing data, n ranges from 26-27

Distribution of ASD group and clinical comparison group scores are displayed on the A scale (Figure 4) and on the B scale (Figure 5).

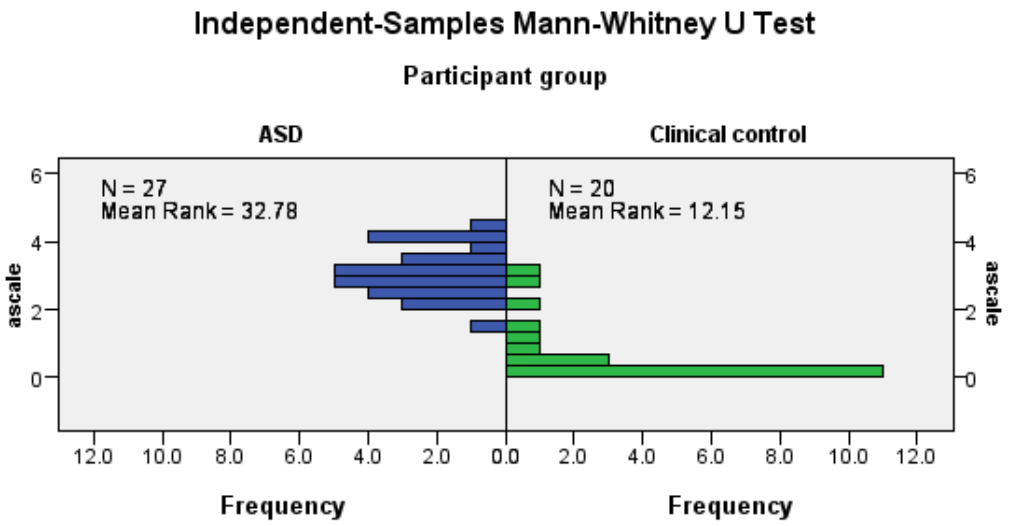

Figure 4. Distribution of ASD and clinical comparison group scores on the A scale of the 3Di-sva full length algorithm

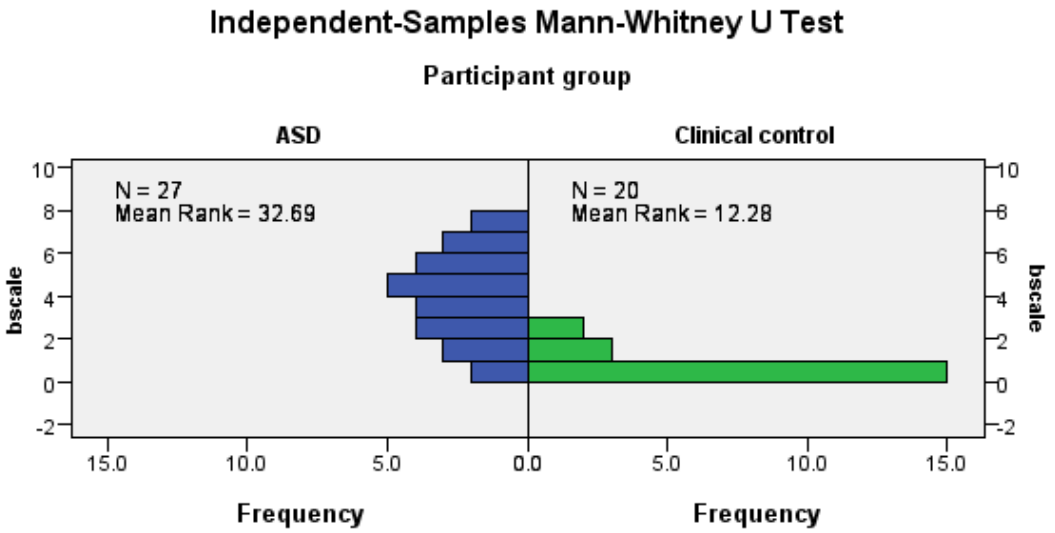

Figure 5. Distribution of ASD and clinical comparison group scores on the B scale of the 3Di-sva full length algorithm

Receiver Operating Characteristic (ROC) analysis

The 3Di-sva full algorithm was able accurately to discriminate between ASD cases and clinical comparison cases for each domain of the dyad of autistic impairments as measured by the A and B scales, with both areas under the curve exceeding 0.93 (Figure 6). The A scale was found to have AUC = .94 (*SE*=.04), *p*<.001, 95% CI [.86, 1.0] and the B scale, AUC = .93 (*SE*=.03), p<.001, 95% CI [.87, 1.0].

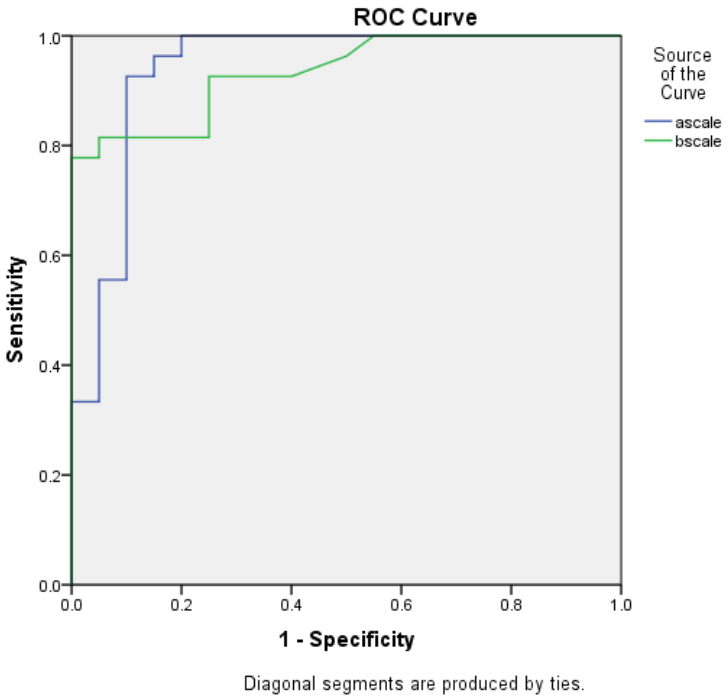

Figure 6. ROC curve of the 3Di-sva full algorithm A scale (AUC= .94) and B scale (AUC=.93)

Optimal cut-offs for the 3Di-sva full algorithm, selected to maximise sensitivity and specificity of the measure, were as follows: a scaled score of 2.1 on the A scale (range 0-6) and a scaled score of 1.0 on the B scale (range 0-8). In order to meet the 3Di-sva full algorithm threshold for a diagnosis of ASD an individual must meet the scoring cut-off on both scales, in accordance with DSM-5 diagnostic

criteria. The proportion of cases correctly identified by the 3Di-sva full algorithm as having ASD is displayed in Table 5.

Table 5

Participant diagnoses identified by the 3Di-sva full algorithm

Participant Group	**3Di-sva diagnosis**	
	ASD	**Non-ASD**
ASD	**23**	**4**
Clinical Comparison	**2**	**18**

These thresholds yielded a sensitivity (the probability that the 3Di-sva full algorithm will correctly detect a positive case of ASD) value of 0.85 (95% CI [.66, .96]) and a specificity (the probability that the 3Di-sva full algorithm will correctly identify non-ASD cases) value of 0.90 (95% CI [.68, .99]). The positive predictive value of the 3Di-sva full algorithm (representing the probability that ASD is present when the algorithm result is positive) was found to be 0.92 (95% CI [.74, .99]) in the current sample. The negative predictive value in this sample (the probability that ASD is not present when the full algorithm yields a negative result) was 0.82 (95% CI [.60, .95]).

Analyses in respect of the 3Di-sva current algorithm

Normality of distribution

The distribution of each 3Di-sva current algorithm scale and subscale was examined by means of visual examination and the Kolmogorov-Smirnov test. Kolmogorov-Smirnov test results are presented in Table 6.

Table 6
Kolmogorov-Smirnov test for normality of distribution of 3Di-sva current algorithm variables

3Di-sva scale / subscale	ASD group	Clinical comparison group	Whole sample
A scale	$D(27)=.12$, $p=.20$	$D(20)=.30$, $p<.001$***	$D(47)=.15$, $p=.01$*
A1	$D(27)=.13$, $p=.20$	$D(20)=.28$, $p<.001$***	$D(47)=.14$, $p=.02$*
A2	$D(27)=.16$, $p=.09$	$D(20)=.31$, $p<.001$***	$D(47)=.13$, $p=.046$*
A3	$D(27)=.16$, $p=.06$	$D(20)=.23$, $p=.006$**	$D(47)=.15$, $p=.011$*
B scale	$D(27)=.10$, $p=.20$	$D(20)=.22$, $p=.014$*	$D(47)=.14$, $p=.016$*
B1	$D(26)=.13$, $p=.20$	$D(20)=.49$, $p<.001$***	$D(46)=.26$, $p<.001$***
B2	$D(27)=.23$, $p=.001$**	$D(20)=.38$, $p<.001$***	$D(47)=.22$, $p<.001$***
B3	$D(27)=.21$, $p=.003$**	$D(20)=.38$, $p<.001$***	$D(47)=.19$, $p<.001$***
B4	$D(26)=.16$, $p=.10$	$D(20)=.36$, $p<.001$***	$D(46)=.23$, $p<.001$***

* deviation from normality significant at $p<.05$ level
** deviation from normality significant at $p<.01$ level
*** deviation from normality significant at $p<.001$ level

As with the full 3Di-sva algorithm, all scales in the clinical comparison group and in the combined group were found to deviate significantly from normality when applying the current algorithm. In the ASD group all 3Di-sva current algorithm scales were distributed normally, other than subscales B2 and B3. Analyses in respect of non-normally distributed variables were carried out by means of non-parametric statistical tests.

Internal consistency

Cronbach's alpha correlation coefficients were computed for each of the scales and subscales of the 3Di-sva current algorithm (Table 7). All scales were found to be in the good to excellent range, excluding the following subscales: B1 ($\alpha = 0.67$; stereotyped repetitive movements or speech), B3 ($\alpha = 0.62$; restricted, fixated interests) and B4 ($\alpha = 0.69$; abnormal sensory response). These three B subscales

fell below the minimum recommended Cronbach's alpha coefficient of 0.7 (Kline, 2000).

Cronbach's alpha for each item of the scales was also examined to assess whether deletion of an item would significantly improve Cronbach's alpha coefficient for the relevant scale. Within the B subscales, item L30 (Does s/he include over-precise information in his/her talk; *r*=.28) from subscale B3 and item I64 (Has [Name] ever seemed unusually interested in things that spin; *r*=.26) from subscale B4 were both found to have low item total correlations. Deletion of item L30 from subscale B3 would have improved Cronbach's alpha (from $\alpha = 0.62$ to $\alpha = 0.71$). Deletion of item I64 from subscale B4 would also have improved Cronbach's alpha (from $\alpha = 0.69$ to $\alpha = 0.74$). However, it was felt that removal of these items would have significantly compromised the content validity of the 3Di-sva current algorithm, by limiting its coverage of DSM-5 diagnostic criteria. Accordingly the items were retained.

Table 7

Internal consistency and interrater reliability of each scale and subscale of the 3Di-sva current algorithm

3Di-sva scale / subscale	Internal consistency (Cronbach's α)	Interrater reliability (ICC)
	N=47‡	**N=28†**
Social communication and interaction ('scale A')	0.95	0.96*
Social emotional reciprocity (subscale A1)	0.83	0.93*
Deficits in non-verbal behaviour used for social interaction (subscale A2)	0.91	0.98*
Deficits in forming, maintaining and understanding relationships (subscale A3)	0.88	0.89*
Repetitive interests ('scale B')	0.92	0.98*
Stereotyped repetitive movements or speech (subscale B1)	0.67	0.97*
Insistence on sameness (subscale B2)	0.87	0.94*
Restricted fixated interests (subscale B3)	0.62	0.92*
Abnormal sensory response (subscale B4)	0.69	0.93*

Note: ‡ Due to missing data: *N* ranges from 31-45 for internal consistency analysis.
† A sample of 29 participant 3Di-sva interviews were assessed for interrater reliability. Due to missing data *N* ranges from 27-28 for this analysis.
* $p < 0.001$

Interrater reliability

Intraclass correlations for the 3Di-sva current algorithm were high, with each of the scales and subscales yielding ICCs in excess of 0.89 (Table 7).

Criterion validity

Mean scores obtained by the ASD group and the clinical comparison group on each 3Di-sva current algorithm scale and subscale are displayed in Table 8.

Table 8
Differences in 3Di-sva current algorithm scores between groups (N=47)

Scale / subscale of the 3Di-sva	Range‡	ASD n=27†	Clinical comparison group n=20	Significance*	Effect size
Social communication and interaction (scale A)	0-6				
Mean (SD)		3.02 (0.93)	0.73 (1.05)	U = 39.00, z = -4.97, $\boldsymbol{p < 0.001}$	r = -0.72
Median		3.10	0.29		
Social emotional reciprocity (A1)	0-2				
Mean (SD)		1.01 (0.32)	0.29 (0.48)	U = 59.50, z = -4.57, $\boldsymbol{p < 0.001}$	r = -0.67
Median		1.10	0.00		
Deficits in non-verbal behaviour used for social interaction (A2)	0-2				
Mean (SD)		0.92 (0.41)	0.18 (0.28)	U = 36.00, z = -5.07, $\boldsymbol{p < 0.001}$	r = -0.74
Median		0.80	0.00		
Deficits in forming, maintaining and understanding relationships (A3)	0-2				
Mean (SD)		1.08 (0.43)	0.27 (0.34)	U = 52.00, z = -4.71, $\boldsymbol{p < 0.001}$	r = -0.69
Median		1.11	0.11		
Repetitive interests (scale B)	0-8				
Mean (SD)		4.17 (2.05)	0.69 (0.83)	U = 31.50, z = -5.14, $\boldsymbol{p < 0.001}$	r = -0.75
Median		4.17	0.33		
Stereotyped repetitive movements or speech (B1)	0-2				
Mean (SD)		0.91 (0.63)	0.08 (0.24)	U = 60.00, z = -4.67, $\boldsymbol{p < 0.001}$	r = -0.69
Median		1.00	0.00		

Scale / subscale of the 3Di-sva	Range‡	ASD n=27†	Clinical comparison group n=20	Significance*	Effect size
Insistence on sameness (B2)	0-2				
Mean (SD)		1.51 (0.68)	0.26 (0.42)	U = 51.50, z = -4.87, $\boldsymbol{p < 0.001}$	r = -0.71
Median		2.00	0.00		
Restricted fixated interests (B3)	0-2				
Mean (SD)		1.07 (0.67)	0.17 (0.28)	U = 59.50, z = -4.66, $\boldsymbol{p < 0.001}$	r = -0.68
Median		1.00	0.00		
Abnormal sensory response (B4)	0-2				
Mean (SD)		0.74 (0.62)	0.18 (0.26)	U = 123.50, z = -3.15, $\boldsymbol{p = 0.002}$	r = -0.46
Median		0.71	0.00		

‡ Higher score signifies greater impairment
† Due to missing data, n ranges from 26-27
* Asymptotic significance values are displayed

Mann Whitney *U* tests show that the ASD group scored significantly higher than the clinical comparison group on all nine of the scales. Effect sizes for both A and B scales are above the .5 threshold for a large effect (Field, 2005), and effect sizes for the subscales all fall within the medium to high range. Population pyramid charts for 3Di-sva current algorithm scores on the A and B scales are displayed in Figures 7 and 8 respectively.

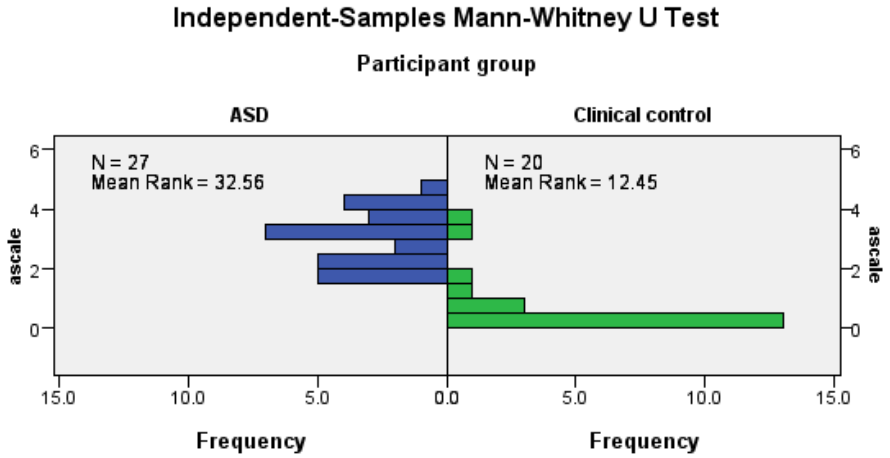

Figure 7. Distribution of ASD and clinical comparison group scores on the A scale of the 3Di-sva current algorithm

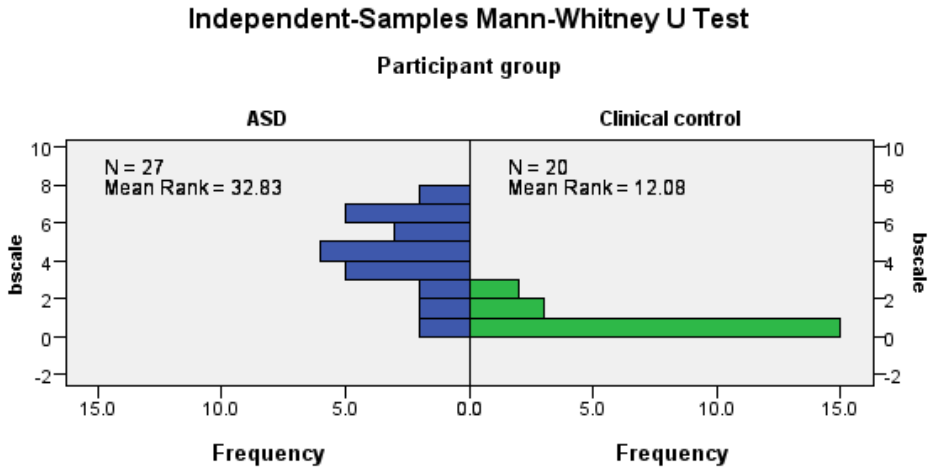

Figure 8. Distribution of ASD and clinical comparison group scores on the B scale of the 3Di-sva current algorithm

ROC analysis

The 3Di-sva current algorithm was able accurately to discriminate between ASD cases and clinical comparison cases on both the A and B scales, with areas under the curve exceeding 0.93 (Figure 9). The A scale was found to have AUC = .93 (SE=.05), p<.001, 95% CI [.84, 1.0] and the B scale, AUC = .94 (SE=.03), p<.001, 95% CI [.88, 1.0].

Optimal cut-offs for the 3Di-sva current algorithm, selected to maximise sensitivity and specificity of the measure, were as follows: a scaled score of 1.5 on the A scale (range 0-6) and a scaled score of 1.9 on the B scale (range 0-8). As with the 3Di-sva full algorithm, an individual must meet the scoring cut-off on both scales in order to qualify for a diagnosis of ASD according to the 3Di-sva current algorithm.

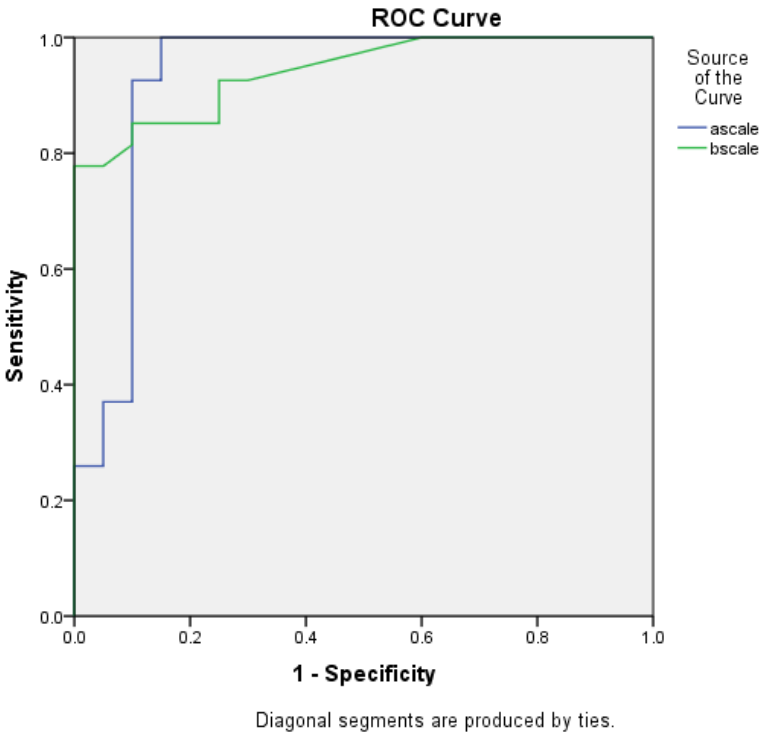

Figure 9. ROC curve of the 3Di-sva current algorithm A scale (AUC= .93) and B scale (AUC=.94)

The proportion of cases correctly identified by the 3Di-sva current algorithm as having ASD is displayed in Table 9.

Table 9

Participant diagnoses identified by the 3Di-sva current algorithm

Participant Group	3Di-sva diagnosis	
	ASD	**Non-ASD**
ASD	**23**	**4**
Clinical Comparison	**1**	**19**

Using these figures, sensitivity of the 3Di-sva current algorithm was calculated at 0.85 (95% CI [.66, .96]) and specificity at 0.95 (95% CI [.75, 1]). The positive predictive value of the 3Di-sva current algorithm was found to be 0.96 (95% CI [.79, 1]) and the negative predictive value was 0.83 (95% CI [.61, .95]).

Discussion

Standardised instruments are needed to facilitate the challenging process of diagnosing ASD in adults. Whereas great improvements have been made over the past 30 years in the identification of ASD in children, research into the assessment process in adults has been somewhat neglected (Bastiaansen et al., 2011; NICE, 2012). In particular, adult-specific informant report measures are an important component of a comprehensive assessment process which collects data from multiple sources. This study examined the psychometric properties of a new informant report measure, the 3Di-sva, in a sample of adults with an established ASD diagnosis and a clinical comparison group of individuals with mental health difficulties and no

history of ASD. The psychometric properties of an abbreviated version of the 3Di-sva algorithm (focusing exclusively on the current functioning of the individual) were also examined.

3Di-sva full algorithm

This study found the full length 3Di-sva to be a reliable measure. The tool demonstrated good interrater reliability when scored by an individual who was blind as to participant group, suggesting the 3Di-sva full algorithm can generate consistent agreement among interviewers. In addition, each of the scales and subscales of the full length 3Di-sva (excluding subscale B1) was found to have acceptable to excellent internal consistency, suggesting the questions in each scale measure the same underlying construct. Subscale B1 (stereotyped or repetitive movements) fell just short of the minimum recommended Cronbach's alpha coefficient of 0.7 (Kline, 2000). However, it is worth noting that this subscale consists of just three items and studies have shown that the number of items in a scale may have a significant impact on Cronbach's alpha, with longer scales tending to have higher values of alpha (e.g. Cortina, 1993). Indeed, all the subscales of the B scale have significantly fewer items than those of the A scale and this may have contributed to the slightly lower internal consistency found for the B subscales. It would be useful to assess whether the addition of further items testing the same underlying concept would improve the internal consistency of the subscales of the B scale without introducing redundant questions.

The inclusion of additional items on the B scale would also help to redress the balance of the interview, which currently asks a great many more questions related to the domain of social communication and interaction than to that of

restricted, repetitive patterns of behaviour. The scoring algorithm tackles this imbalance by adjusting subscale scores to ensure that each subscale carries equal weight. However, arguably it would improve the content validity of the measure if the A and B scales were more balanced in terms of volume of items, thereby more accurately reflecting DSM-5. Notably, other measures used in the assessment of ASD also reflect this imbalance. For example, the ADI-R (Lord et al., 1994) has 29 items to measure social communication issues and only eight items to measure restricted, repetitive behaviours. This suggests there is a general need for further research into the measurement of restricted, repetitive behaviours and interests in ASD.

The full length 3Di-sva was found to have good general criterion validity as demonstrated by the difference in scores obtained by participants with an established ASD diagnosis compared to those obtained by clinical comparison participants. ASD participants scored significantly higher than clinical comparison participants on all scales and subscales of the measure and large effect sizes were found. The measure was able accurately to distinguish between ASD cases and clinical comparison cases as demonstrated by the high Areas under the Curve for each of the A and B scales. Sensitivity (0.85) and specificity (0.90) of the measure suggest it is capable of correctly distinguishing between positive cases of ASD and clinical comparison (i.e. non-ASD) cases the majority of the time. Given the potential overlap in symptomatology between ASD and the mental health difficulties experienced by participants in the clinical comparison group, the task set for the 3Di-sva in this study was a reasonably challenging one, comparable to the task facing clinicians working in adult mental health services. Nevertheless, the majority of participants in the clinical comparison group were not suspected of having ASD at

the time of assessment. A more ecologically valid, task in terms of assessing the validity of the 3Di-sva as a diagnostic tool, would be to assess its ability to discriminate between adults, all of whom were suspected of having ASD but some of whom were established as having other mental health difficulties underlying their symptomatology.

The 3Di-sva full algorithm failed to identify four individuals with ASD. For the purposes of assessing sensitivity and specificity, consistent with DSM-5 diagnostic criteria, an individual was only classified as positive for ASD if he or she reached the appropriate threshold on each of the A (social communication and interaction) and B (restricted repetitive behaviour, interests or activities) scales, representing the two core domains of ASD symptomatology. Two of these four false negative cases narrowly missed the threshold on the A scale but reached the threshold on the B scale. One case missed the threshold on both scales and one case missed only the B scale cut-off. These findings highlight the challenge involved in diagnosing complex cases of ASD and the need for multiple components in a comprehensive assessment process, including direct observation of an individual's behaviour wherever possible (NICE, 2012).

The full length 3Di-sva incorrectly identified two clinical comparison cases (scoring above the cut-off point on both A and B scales) as having ASD. Both these individuals were assessed for ASD by one of the specialist ASD clinics participating in this study but were given differential diagnoses after ASD had been ruled out. One was diagnosed with depression, the other with social anxiety disorder. It is perhaps not surprising that individuals who present with so many symptoms consistent with ASD that they are referred to a specialist ASD clinic for assessment should prove particularly challenging for the measure to identify correctly. Caron

and Rutter (1991) highlight the fact that certain behaviours may represent non-specific indicators of psychopathology generally, with increased severity of a disorder often being associated with an increase in the number of such non-specific indicators. Both depression and social anxiety disorder are associated with forms of behaviour which also appear in the diagnostic criteria for ASD (DSM-5; APA, 2013a). Symptoms of depression which are also characteristic of ASD include social withdrawal, flattened affect, limited facial expression and a decrease in the volume, amount and inflexion of speech (e.g. DSM-5; APA, 2013a; Hofvander et al., 2009). ASD is listed as a differential diagnosis for social anxiety disorder in DSM-5 and it is acknowledged that key features of social anxiety disorder (social communication difficulties and fear of social situations) are also characteristic of ASD (APA, 2013a). Again, this finding highlights the need, in clinical practice, for a broad assessment process involving a multidisciplinary team of clinicians who are able to debate complex presentations and reach clinical consensus as to whether a diagnosis is appropriate or helpful (NICE, 2012).

This study found the full length 3Di-sva to be relatively quick to administer with interviews taking between 15 and 75 minutes to conduct. Training in the use of the 3Di-sva appeared to be swift and efficient with each researcher or clinician receiving around an hour of guidance prior to first administration of the measure. Importantly, brief training in respect of how to score the 3Di-sva appeared to be satisfactory for the less experienced psychology undergraduate who assisted the researchers by scoring recordings of the interviews for the assessment of interrater reliability. Notably, interviews were carried out successfully both in person and over the telephone, suggesting the tool may have particular utility in clinical practice where informants are not always able to attend in person.

3Di-sva current algorithm

This study also examined the psychometric properties of the 3Di-sva current algorithm, an abbreviated version of the 3Di-sva algorithm which only includes questions about the current functioning of the individual. Whilst DSM-5 criteria state that symptoms of ASD must have been present in early childhood, in clinical practice it is not always possible to involve a family member, or other informant who has known the adult well since childhood, in the assessment process. As such, it was felt to be pragmatic to assess the psychometric properties of this abbreviated version of the scoring algorithm suitable for use with an informant who can only speak as to the individual's current functioning.

The 3Di-sva current algorithm was also found to be a reliable measure. Interrater reliability was good. The A and B scales were found to have excellent internal consistency, as were all three A subscales and subscale B2. Subscales B1, B3 and B4 fell below the recommended Cronbach's alpha coefficient of 0.7 (Kline, 2000). Again, the very small number of items in these scales, further reduced by removal of questions relating to early development, may have impacted on the value of Cronbach's alpha (Cortina, 1993).

The 3Di-sva current algorithm demonstrated good general criterion validity. As with the full algorithm, ASD participants scored significantly higher than clinical comparison participants on all scales and subscales of the measure, with large effect sizes on the A and B scales and medium to large effect sizes on all subscales. High Areas under the Curve for each of the A and B scales demonstrated the current algorithm's ability accurately to distinguish between ASD cases and clinical comparison cases. Sensitivity (0.85) and specificity (0.95) of the current algorithm

suggest it is capable of correctly distinguishing between positive cases of ASD and non-ASD cases the majority of the time. The clinical comparison group in this study included two younger sibling informants who were unable to answer 3Di-sva questions regarding the individual's childhood, however the vast majority of data were collected from informants (such as parents) who had known the individual well as a child. In future research it would be important to assess the psychometric properties of the 3Di-sva current algorithm when employed solely with informants who did not know the individual in childhood, for example, friends or non-familial carers.

The 3Di-sva current algorithm failed to identify four individuals with ASD. All of these misdiagnosed cases reached the cut-off for the A scale and missed the threshold on the B scale. Research suggests there exists a group of individuals who have significant social communication and interaction difficulties but fail to manifest restricted, repetitive patterns of behaviour or interests to a clinical degree (e.g. Mandy & Skuse, 2008; Walker et al., 2004). DSM-5 created a new diagnosis of Social Communication Disorder to capture such cases but also states that full ASD diagnostic criteria may be met by an adult where such restricted, repetitive interests were manifest in childhood even if they are not present at the time of assessment (APA, 2013a). This raises the possibility that the 3Di-sva current algorithm, focusing as it does exclusively on current presentation in adults, may be missing individuals who no longer display clinically significant levels of restricted, repetitive behaviour symptoms. Whilst there is evidence of a modest degree of improvement in ASD symptoms, including those related to restricted and repetitive behaviours, in adolescence and adulthood (e.g. Seltzer, Shattuck, Abbeduto & Greenberg, 2004), studies suggest that the improvement may in fact be more limited in this domain than

in the area of social communication (e.g. Taylor & Seltzer, 2010). In the present study, two of the misdiagnosed participants were also incorrectly excluded by the full algorithm, suggesting these may have been particularly subtle ASD presentations requiring additional means of assessment. The remaining misdiagnosed participants may have manifested more severe restricted, repetitive behaviours in childhood, emphasising that access to information about an individual's past history remains important. Where there is no available informant in possession of such historical information, documentary evidence, such as school reports, may be sought (NICE, 2012). A further possibility is that restricted, repetitive behaviours may become more subtle as individuals age and that items in the 3Di-sva were not sophisticated enough to capture these subtleties. Studies suggesting that restricted repetitive behaviours may become less frequent and less severe among older individuals nevertheless show that such behaviours do continue to manifest in older age (Esbensen, Seltzer, Lam & Bodfish, 2009). Further research into the presentation of restricted, repetitive behaviours in adults with ASD as compared with typically developed adults would be valuable and may aid the development of interview questions particularly suited to an adult population.

Limitations and future directions

The present study investigates the psychometric properties of the 3Di-sva in a sample of adults with an established ASD diagnosis and a comparison group of individuals with a range of different mental health difficulties. Initially, the researchers sought two separate clinical comparison groups of (1) individuals with psychotic disorders and (2) individuals with depression and anxiety disorders, to allow for separate statistical analyses. However, as it was not possible to recruit separate samples of sufficient size, these groups were collapsed into one comparison

group and recruitment was extended to include a broader range of mental health diagnoses, including personality disorders. In clinical practice, it is important to rule out potential differential diagnoses that can give rise to similar symptoms to ASD. A limitation of the present study is that very few participants in the clinical comparison group were genuinely suspected of having ASD at the time of assessment. Such a clinical comparison group would have provided a more ecologically valid task for the 3Di-sva, in terms of posing a particular challenge for the tool in accurately identifying true cases of ASD. An important direction for future research would involve testing the psychometric properties of the 3Di-sva in the context of a group of individuals all of whom have symptoms consistent with ASD but only some of whom are diagnosed with the condition. Future research could also address the heterogeneity of the comparison group here by recruiting groups with specific separate clinical diagnoses and comparing the psychometric properties of the 3Di-sva in these groups. This would provide valuable information as to the ability of the 3Di-sva to differentiate between individuals with ASD and individuals with specific mental health disorders, rather than mental health difficulties in general. For example, adult participants experiencing negative symptoms associated with schizophrenia have been found to be particularly difficult to distinguish from individuals with ASD when administering the ADOS module 4 (Bastiaansen et al., 2011) and it would be interesting to investigate the 3Di-sva's ability to differentiate between these particular populations.

It is also important to explore the psychometric properties of the 3Di-sva in a population of individuals who have never received a DSM diagnosis of neurodevelopmental or mental health difficulties. As previously mentioned, this research has been carried out in a concurrent study (Clarke, 2015).

In deciding whether or not to provide a diagnosis of ASD, the clinical teams at the ASD clinics participating in this study did take into consideration information collected during the 3Di-sva interview process, such information forming part of all data available to the team relating to an individual being assessed. It could be argued that such consideration constitutes a limitation in this study because it creates the risk of circularity. However, this risk was mitigated by imposing an inclusion criterion that all participants in the ASD group must meet criteria for ASD as assessed specifically by the ADOS and by the fact that the 3Di-sva scoring algorithm was not utilised at all in the diagnostic decision-making process. It would be beneficial, in future studies, to make use of the ADI-R, both as a means of obtaining collateral information about the individual as part of the assessment process (rather than the 3Di-sva) and as a means of further investigating the criterion validity of the 3Di-sva by comparing results with those of an alternative 'gold standard' informant report measure.

Clarke (2015) investigated the correlation between the 3Di-sva and the ADOS module 4, however the relatively small sample size in that study may have limited the findings and further exploration is warranted. Construct validity of the 3Di-sva could be tested in future research using factor analysis.

A further limitation of this study was the failure to assess test retest reliability, due to limited time and resources. It will be important in the future to evaluate the stability of 3Di-sva diagnoses across time by re-assessing individuals after an appropriate period has elapsed.

The participants in the clinical comparison group in this study (excluding the four participants initially assessed by a specialist ASD clinic) were not assessed for

ASD by means of a measure validated for use with adults (such as, the ADI-R, the ADOS module 4, or the RAADS). Again this was due to limited resources in the present study. Future research could address this potential confounding factor by inviting comparison participants to engage in a comprehensive ASD assessment and offering greater incentives to compensate for the time and inconvenience involved in such a process.

The sample size in this study is relatively small and it would be valuable for future research to expand on the number of participants included here. For example, the size of the sample may have had an impact on the accuracy of the sensitivity and specificity values reported here. In addition, it was not possible to evaluate the internal consistency of the 3Di-sva scales and subscales for each individual group of participants; values reported here are for the entire sample. This was due to there being insufficient variance within the groups (in particular, within the comparison group) on certain subscales, whereas a larger sample may have contributed to greater variance. Nevertheless the number of participants here is similar to that of samples studied in research examining the psychometric properties of other diagnostic tools (e.g. ADI-R; Lord et al., 1994) and the size was sufficient for the purpose of detecting the substantial differences between groups found here with large effect sizes. A relatively small proportion (n=10) of the ASD group interviews were recorded for the purposes of assessing interrater reliability. Future research would benefit from inclusion of greater numbers of participants in the interrater reliability assessment.

Interviews in this study were administered both in person and over the telephone, however no analysis was conducted investigating any difference in outcome according to means of administration. Such analysis would have been

difficult to carry out in this research due to the small proportion of interviews carried out in person in the clinical comparison group (n=3) and, conversely, the small proportion of interviews known to have been carried out over the telephone in the ASD group (n=5). A further potential confound that would be useful to investigate in future research is the identity of the informant being interviewed. In the present study all known informants in the ASD group were mothers, as were the majority of informants in the comparison group (n=14), meaning that there were insufficient numbers of non-maternal informants to allow for meaningful comparison of outcome. The 3Di was specifically designed to minimise respondent bias, with questions clustered according to areas of function rather than according to diagnostic criteria (Skuse et al., 2004). It is also a highly structured measure which should lessen any effect of method of administration. However, future research involving a larger sample size could usefully examine any impact of such factors.

Finally, given that intellectual disability has been specifically identified as a differential diagnosis to be considered when assessing an individual for ASD (NICE, 2011) and is a potential coexisting condition with some 25% of individuals with ASD also diagnosed as having an IQ below the normal range (Medical Research Council, 2001), it would be important for future studies to assess the psychometric properties of the 3Di-sva in an intellectual disability population.

Conclusions and implications

In summary, this study provides promising evidence to suggest that the 3Di-sva is a well validated, reliable informant report instrument for the diagnosis of autism spectrum disorders in adults. It has been shown adequately to discriminate ASD from other mental health difficulties in an adult population, although it is

important to acknowledge that only a very small proportion of participants in the clinical comparison group were suspected of having ASD at the time of assessment. Given the association between ASD and a range of other disorders, such as depression and anxiety, and the overlap in symptomatology of ASD and other conditions, it is vital that assessment tools be capable of disentangling ASD symptoms from other factors in a complex clinical presentation. It will be very important in future research to assess the psychometric properties of the 3Di-sva in a sample of individuals, all of whom have symptoms consistent with ASD. Such research will need to ensure that the tool is capable of distinguishing true cases of ASD from cases where ASD-like symptoms are better explained by other mental health difficulties.

The 3Di-sva is one of the first tools to be structured specifically according to DSM-5 criteria, assessing the full range of symptoms described and providing a valid DSM-5 diagnosis (APA, 2013a). It is also simple to use, requiring only an hour of training prior to first administration. It is time efficient relative to other informant report measures, enhancing its utility in resource-strapped clinical settings.

This research, in conjunction with Clarke (2015), constitutes an important first step in establishing the validity and reliability of this new informant report measure for use with adults. Given the paucity of psychometric evidence for use in adult populations reported by NICE (2012) for existing informant report measures, the ADI-R, AAA, ASDI and DISCO, there is a need for novel tools which are valid and reliable. It is hoped that the 3Di-sva may constitute a useful addition to the battery of measures required to carry out a 'gold standard' comprehensive assessment of adults with complex presentations, alongside observational tools, such as the ADOS, and self-report tools, such as the RAADS.

Future research is needed to provide further evidence of the psychometric properties of the 3Di-sva, including test-retest reliability, criterion validity and studies benefitting from larger sample sizes in which all individuals were suspected of having ASD at the time of assessment. However, this research represents a promising foundation upon which to base further research into the utility of this measure.

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PART 3: CRITICAL APPRAISAL

Introduction

This critical appraisal provides additional reflection on aspects of the research process which have been particularly thought-provoking. It begins with a reflection on elements of my personal clinical experience working with individuals with autism spectrum and other mental health disorders, and of the challenge involved in untangling complex presentations in the clinic. It goes on to consider the ways in which such experiences contributed to the literature review and the research project, as well as the evolution of my personal perspective on both research and clinical practice through the research process. Some of the methodological challenges encountered throughout this process will also be considered.

Clinical experiences of autism spectrum disorder and psychosis

My experiences as a trainee clinical psychologist working across psychosis services in an NHS mental health trust first drew my attention to the possibility of an overlap or association between autism spectrum disorder (ASD) and psychosis. I became aware of a proportion of individuals receiving treatment for psychosis in adult psychiatric services who were also observed to present with features resembling ASD. As a clinician, I considered a number of possible factors that might explain this.

Certain symptoms of psychosis (possibly exacerbated by side effects associated with anti-psychotic medication) might be mistaken for ASD, for example, social withdrawal, impaired reciprocal social interaction, monotonous tone of voice, unusual or reduced eye contact and gesture, minimal response to other people's facial expressions and a tendency to miss social cues. Alternatively, unrecognised symptoms of ASD may have been misconstrued as psychosis, potentially leading to a

stigmatising diagnosis and the inappropriate administration of powerful anti-psychotic medication associated with significant side effects and risks to health.

My experiences of working on a child psychiatric inpatient unit further highlighted the risk of misattribution of features of ASD to a psychotic disorder in a child population. A number of children were referred to the unit with a diagnosis of ASD and additional concerns around the possibility of psychotic symptoms. Detailed observation of these children was carried out in a range of contexts to try to assess whether their behaviour was suggestive of psychosis. In the vast majority of cases, whilst there was behaviour that might have been considered 'unusual', the clinical consensus was that it could be explained by ASD alone. Children may have appeared preoccupied without obvious reason, seemed particularly caught up in an imaginary world, shown unusual gaze patterns, or mumbled to themselves, but there was often no clear evidence of psychosis. Rather they appeared to be focused on stereotypic preoccupations, hyper or hypo sensitive to sensory stimuli (e.g. gazing intently at a speck of dust caught in a beam of sunlight), avoidant of, and uncomfortable with, all aspects of social interaction on the unit, or anxious in general (e.g. Dossetor, 2007).

A further possibility was that adults with undiagnosed ASD might be presenting in psychiatric services with co-occurring psychotic symptoms. If so, could this be explained in terms of ASD and psychosis sharing the same aetiological underpinnings, or did ASD convey a particular risk of developing psychotic symptoms? Moreover, might the failure to diagnose this neurodevelopmental disorder in childhood itself have contributed to these individuals experiencing hardship, misunderstanding, loss of opportunity and increased vulnerability to comorbid mental health difficulties?

From personal experience to systematic literature review

These personal clinical experiences highlighted the importance of gaining a detailed understanding of the relationship between ASD and psychosis in order to enhance evidence based approaches to assessing and supporting individuals with complex presentations in the clinic. An investigation into existing literature estimating rates of co-occurrence of the two disorders seemed a logical next step.

I was immediately struck by the wide variability in methodology of studies investigating the co-occurrence of these disorders and the considerable risk of bias associated with many current estimates. Moreover, whilst my search terms identified a significant number of studies for screening by hand, as I progressed with this process it became apparent that some studies may have inadvertently been excluded from the review due to the broader term 'psychopathology' being used by researchers to describe the subject of their research. This reflected a tendency for many studies reviewed not to be investigating co-occurrence of ASD and psychosis as a primary research question which issue, in itself, could be argued to carry a risk of bias.

My original personal experience of the questions around co-occurrence was in the context of a psychosis population. However, in carrying out this review, it was notable that research into the prevalence of ASD in individuals with psychosis appeared to be particularly unreliable due to a range of methodological and nosological problems. Whilst I felt able to draw tentative conclusions as to the likely prevalence of psychosis in an ASD population, I struggled to reach any solid conclusions for the prevalence of ASD among individuals with psychosis.

Studies varied as to the included or excluded autism spectrum diagnoses as set out, for example, in DSM-IV. Future studies would benefit from applying a comprehensive 'autism spectrum disorder' criterion for case ascertainment, as now set out in DSM-5. Many studies utilised non-validated screening tools, or screened by means of an initial record review, prior to carrying out any detailed assessment for ASD, acknowledging that there were simply not the resources to carry out the lengthy process involved in such assessments with every participant in the sample. Even then, most studies failed to use an assessment tool recommended for use with adults by NICE guidelines. This struck me as contrasting with the formal diagnostic procedures for ASD utilised in a specialist adult ASD service (such as the clinics where we had recruited our ASD group for the major research project). A further practical difficulty posed by this particular population is that individuals with psychosis may be too acutely unwell to assess directly by means of an observation measure such as the ADOS, but it seemed that many individuals participating in the included studies did not have a close relative available to complete an informant report measure of functioning since early childhood. This latter issue proved only too pertinent to my own empirical research.

The range of estimates of prevalence of psychosis in an ASD population was even broader than that of ASD in individuals with psychosis (0% to 61.5% as opposed to 0.8% to 27%). However, the process of unpicking sources of potential bias, so as to allow for meaningful comparison of figures, seemed a little less challenging. Methods employed in the ascertainment of ASD cases appeared to be more reliable (although, again, a minority stipulated use of a NICE-recommended tool). In ascertaining cases of psychosis, some of the studies utilised a range of methods commonly seen in the clinic, including direct clinical interview, symptom

checklists, informant collateral interview and some structured diagnostic tools. However, of underlying significance seemed to be the fact that the identification of psychosis in individuals with ASD can be difficult (for all the reasons outlined in the review) and that there are no tools designed specifically for this task.

The literature review highlighted the practical barriers to carrying out meticulous population-based studies investigating this issue. Future investigations of rates of co-occurrence of ASD and psychosis might involve large scale longitudinal studies aiming routinely to invite all individuals diagnosed with ASD for follow-up as they progress into adulthood, including a comprehensive mental health assessment.

From personal experience to empirical research

The clinical experiences of adult psychiatric services recounted above drew my attention to the limited service provision for individuals presenting in adult services with suspected ASD. In the context of general adult mental health services there seemed to be a lack of expertise or resource available to carry out the appropriate ASD assessments. In particular, measures constituting the 'gold standard' in assessing ASD in adults, such as the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000) and the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter & Le Couteur, 1994), required specialist and costly training unavailable to clinicians working in general adult services. Not only was there a lack of ready access to such measures in adult mental health services but assessment by specialist adult ASD services was subject to long waiting lists. I was aware that the UK government had published statutory guidance (Department of Health, 2010) setting out recommendations for a clear and consistent pathway to diagnosis of ASD

in adults. However, with increased financial pressure on the National Health Service in the face of an effective budget freeze and cuts to social care services over recent years (The King's Fund, 2015), it seemed that in practice there was some way to go before such plans would be properly implemented.

It was against this backdrop that the need for additional efficient and effective tools for the assessment of ASD in adults presented itself to me. I embarked upon the research project convinced of the clinical relevance and importance of the study. Having seen the deficiencies for myself, and specifically in the context of more generalised adult mental health services, I was, perhaps naively, convinced that the pressing purpose of the research would be easily conveyed to services and potential participants alike.

The challenges involved in recruiting a clinical comparison group

Whilst I anticipated that it would be challenging to recruit individuals with mental health difficulties – and their parents – to our study, the full extent of the challenge that confronted us took me by surprise. My fellow joint project researcher and I had originally planned to recruit two separate clinical comparison groups, (i) psychotic disorders and (ii) affective disorders, to allow for separate, disorder-specific, statistical analyses. However, it soon became apparent that the recruitment of two groups of sufficient size would prove impossible in the time available to us. Firstly, we were we trying to persuade individuals with mental health difficulties other than ASD to participate in a project researching a neurodevelopmental disorder with which they had no personal connection. Secondly, we were trying to persuade these individuals to invite a parent or other relative to answer detailed and potentially intrusive questions about them – relating to their childhood and current presentation. Finally, assuming we could persuade the individual to agree to their relative being

approached in this way, we needed to persuade this relative to give up the time needed for the interview to take place (albeit this could be over the telephone). This proved to be a Herculean task.

It proved particularly difficult to recruit individuals to the psychosis comparison group. I had been warned prior to commencing the project that this group of individuals was potentially very difficult to recruit. In particular, clinical experience suggested that a significant proportion of these individuals may not be on good terms with parents or other family members capable of completing the full 3Di-sva interview, including questions on early childhood. However, working closely with the pathway lead for inpatient and acute psychology in the NHS Trust where I was recruiting, we devised numerous strategies that we thought would encourage participation. This included close liaison with a number of teams across the Trust, many hours spent sitting in clinic waiting rooms chatting to individuals passing through and an offer to run brief psychoeducation workshops for carers of individuals with psychosis, in the hope of recruiting family members and winning favour with stretched NHS teams. We also increased the compensation paid to individuals and their relatives from a £5 to a £10 voucher each, in the hope of speeding up recruitment. Whilst this did help, it was insufficient to encourage the participants needed to make up two separate clinical comparison groups. We were forced to collapse the two groups into one broad clinical comparison group and extend recruitment to include a broader range of mental health diagnoses, including personality disorders.

Studies investigating the issues which influence recruitment to mental health research have highlighted factors taken into consideration by individuals deciding whether to participate, and by health care professionals deciding whether to

recommend a study to their patients. A key factor in this decision making process is an assessment of whether involvement in the study will be beneficial to the individual concerned, for example, whether the project will add to the care being provided to the individual (e.g. Bucci, Butcher, Hartley, Neil, Mulligan & Haddock, 2015; Hughes-Morley, Young, Waheed, Small & Bower, 2015). Our study could not be argued to add to, or facilitate, the care of individuals in the clinical comparison group with mental health needs. The development and validation of an effective, user-friendly tool for the assessment of ASD in a clinical population may prove to be a valuable asset in the care of individuals presenting to services with complex presentations and uncertainty as to symptoms of ASD or mental health difficulties or both. However, such individuals were excluded from the present study unless concerns as to ASD had been specifically ruled out by clinical consensus at the ASD clinic. In their systematic review of qualitative studies investigating factors affecting recruitment into depression trials, Hughes-Morley and colleagues (2015) did identify a sub-theme of 'altruism' as a factor reported to impact patients' decision as to whether to enrol in trials. Whilst it was found that patients did want to help others and contribute to the body of research, they were far more likely to participate if they also felt that they were helping themselves in the process (Hughes-Morley et al., 2015). In the present study, we were asking potential participants to enrol in a study that would be of no direct benefit to them and to contribute to knowledge around a field that had little or nothing to do with their own difficulties.

Another barrier to participation identified by the literature is, understandably, the question of how acutely unwell or distressed the individual is, or is perceived to be by a 'gate-keeping' clinician (Bucci et al., 2015; Hughes-Morley et al., 2015). This may be a particular issue when dealing with a psychosis population attending

secondary care services, with individuals potentially facing ongoing challenging mental health symptoms, unpleasant side effects of medication, social isolation and significant adversity.

The experience of attempting to recruit individuals with psychosis (and other mental health difficulties) to this study left me wondering by what means such barriers to recruitment might be overcome, in order to progress important research. We did not have the opportunity, in the present study, to involve service users in the design of the research, or to consult with them as to methods of recruitment. Future research might explore the views of service users with diagnoses of ASD or psychosis, or both. I also reflected on the ideal of the scientist-practitioner model in the reality of a stretched National Health Service. It seemed to me that, in an ideal world, clinical psychologists working in adult mental health services would be the very individuals researching tools such as the 3Di-sva and (subject to appropriate ethics) incorporating research assessments more seamlessly into their clinical practice. However, I was aware that, with resources so scarce in mental health services, this was perhaps unrealistic.

Methodological impact of recruitment difficulties

The recruitment difficulties referred to above inevitably had an impact on the sample of clinical comparison participants in this study. On the one hand, our clinical comparison group was heterogenous. Individuals were diagnosed with a broad range of mental health difficulties and it was not possible to investigate the ability of the 3Di-sva to distinguish between ASD and particular symptoms associated with a specific diagnosis. As such, any potential variations in the validity of the 3Di-sva depending on the specific clinical population being assessed could not

be identified. On the other hand, the participants in this group could be argued to be somewhat homogenous. For example, they were likely to be the 'less unwell' individuals in a clinical population and were all in sufficiently close contact with family members to trust them to engage in a detailed, personal interview.

Clinicians working in mental health services may, of course, work with individuals presenting with a broad range of difficulties, and in this sense it is argued that we have set the 3Di-sva an ecologically valid task in the present study. Nevertheless, in potentially failing to recruit those individuals with more severe, complex presentations, experiencing social isolation and ruptured family relations, we may have excluded precisely those individuals posing the greatest challenge to clinicians when it comes to distinguishing mental health difficulties from ASD.

Increasing specificity of the 3Di-sva in an ASD clinic context?

It was notable that, utilising the optimal cut-off points on both A and B scales, selected to maximise sensitivity and specificity of the measure based on the data in this project, the 3Di-sva failed to identify correctly as clinical comparison cases two participants who had previously been referred to the ASD assessment services with suspected ASD. These individuals had been given differential diagnoses after a comprehensive assessment process had ruled out the possibility of ASD. It is perhaps unsurprising, given this context, that the cut-off points selected in this study rendered the measure a little too sensitive for these individuals. This led my fellow joint project researcher and I to reflect on the possibility of altering the cut-off points of the 3Di-sva depending on clinical setting and need. For example, in an ASD clinic setting it might prove useful to increase the specificity of the measure, whereas in a general mental health setting sensitivity may be more of a priority, such

that individuals with suspected ASD might be flagged as needing a comprehensive assessment in a specialist service.

Concluding remarks

Whilst completing this thesis, I have learnt a huge amount about the process of carrying out both literature reviews and empirical research projects. In reviewing the literature around co-occurrence of ASD and psychosis, I was able to explore existing research considering the very challenges I had experienced in clinical practice assessing adults with complex presentations. This provided an invaluable context for the empirical research validating the use of an ASD assessment tool in a clinical setting, as well as highlighting some of the challenges I was to face in recruiting participants to my clinical comparison group. The experience of completing the research project, notwithstanding the many obstacles in my path, and thereby contributing to the validation of this new, efficient measure for the assessment of ASD in adults, has reaffirmed for me the importance of persevering with such projects. Ultimately, I have a genuine sense that we have added value to the field of knowledge around ASD in adults and that we have taken steps to redress the imbalance in the breadth and quality of ASD assessment procedures available in adult services as compared to child.

My personal experience of carrying out a joint research project has been extremely rewarding and I would recommend this to UCL trainee clinical psychologists considering this option. The opportunity to share the burden of aspects of the project, such as obtaining NHS REC approval, preparing participant documentation, recruiting participants and deciding upon statistical analyses, has been invaluable. In particular, having an ally with whom to share the challenges and

successes of this process at every turn was extremely beneficial to me and undoubtedly contributed to a richer experience over all.

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Appendices

APPENDIX A:

Search terms

Medline Search Terms

	Terms
1	autis*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
2	asd.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3	asperger*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4	pervasive developmental disorder.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5	pdd.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6	1 or 2 or 3 or 4 or 5
7	child development disorders, pervasive/ or asperger syndrome/ or autistic disorder/
8	6 or 7
9	psychosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10	psychotic.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11	schizophren*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12	9 or 10 or 11
13	psychotic disorders/ or schizophrenia/ or schizophrenia, catatonic/ or schizophrenia, disorganized/ or schizophrenia, paranoid/ or shared paranoid disorder/
14	12 or 13
15	8 and 14
16	limit 15 to (english language and humans)

PsychINFO Search Terms

	Terms
1	autis*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
2	asd.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3	asperger*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
4	pervasive developmental disorder.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
5	pdd.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
6	1 or 2 or 3 or 4 or 5
7	pervasive developmental disorders/ or aspergers syndrome/ or autism/
8	6 or 7
9	psychosis.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
10	psychotic.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
11	schizophren*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
12	9 or 10 or 11
13	exp psychosis/
14	12 or 13
15	8 and 14
16	limit 15 to (human and english language)

APPENDIX B:

Risk of Bias Tool

Appendix 1: Risk of Bias Tool

Name of author(s):_____ Year of publication:_____

Name of paper/study:-

_____

_____

This tool is designed to assess the risk of bias in population-based prevalence studies. Please read the additional notes for each item when initially using the tool. Note: If there is insufficient information in the article to permit a judgement for a particular item, please answer **No (HIGH RISK)** for that particular item.

Risk of bias item	Criteria for answers (please circle one option)	Additional notes and examples
External Validity		
1. Was the study's target population **a close representation** of the national population in relation to relevant variables, e.g. age, sex, occupation?	• **Yes (LOW RISK):** The study's target population was a close representation of the national population. • **No (HIGH RISK)**: The study's target population was clearly NOT representative of the national population.	The **target population** refers to the group of people or entities to which the results of the study will be generalised. Examples: • The study was a national health survey of people 15 years and over and the sample was drawn from a list that included all individuals in the population aged 15 years and over. The answer is: **Yes (LOW RISK).** • The study was conducted in one province only, and it is not clear if this was representative of the national population. The answer is: **No (HIGH RISK).** • The study was undertaken in one village only and it is clear this was not representative of the national population. The answer is: **No (HIGH RISK).**
2. Was the sampling frame a **true or close representation** of the target population?	• **Yes (LOW RISK):** The sampling frame was a **true or close** representation of the target population. • **No (HIGH RISK)**: The sampling frame was NOT a **true or close** representation of the target population.	The **sampling frame** is a list of the sampling units in the target population and the study sample is drawn from this list. Examples: • The sampling frame was a list of almost every individual within the target population. The answer is: **Yes (LOW RISK)**. • The cluster sampling method was used and the sample of clusters/villages was drawn from a list of all villages in the target population. The answer is: **Yes (LOW RISK)**. • The sampling frame was a list of just one particular ethnic group within the overall target population, which comprised many groups. The answer is: **No (HIGH RISK).**
3. Was some form of **random selection** used to select the sample, OR, was a census undertaken?	• **Yes (LOW RISK):** A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). • **No (HIGH RISK)**: A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.	A census collects information from every unit in the sampling frame. In a survey, only part of the sampling frame is sampled. In these instances, random selection of the sample helps minimise study bias. Examples: • The sample was selected using simple random sampling. The answer is: **Yes (LOW RISK)**. • The target population was the village and every person in the village was sampled. The answer is: **Yes (LOW RISK)**. • The nearest villages to the capital city were selected in order to save on the cost of fuel. The answer is: **No (HIGH RISK).**
4. Was the likelihood of **non-response bias minimal?**	• **Yes (LOW RISK):** The response rate for the study was >/=75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders • **No (HIGH RISK)**: The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	Examples: • The response rate was 68%; however, the researchers did an analysis and found no significant difference between responders and non-responders in terms of age, sex, occupation and socio-economic status. The answer is: **Yes (LOW RISK)**. • The response rate was 65% and the researchers did NOT carry out an analysis to compare relevant demographic characteristics between responders and non-responders. The answer is: **No (HIGH RISK)**. • The response rate was 69% and the researchers did an analysis and found a significant difference in age, sex and socio-economic status between responders and non-responders. The answer is: **No (HIGH RISK)**.

Internal Validity		
5. Were data collected **directly from the subjects** (as opposed to a proxy)?	• **Yes (LOW RISK):** All data were collected directly from the subjects. • **No (HIGH RISK)**: In some instances, data were collected from a proxy.	A proxy is a representative of the subject. Examples: • All eligible subjects in the household were interviewed separately. The answer is: **Yes (LOW RISK)**. • A representative of the household was interviewed and questioned about the presence of low back pain in each household member. The answer is: **No (HIGH RISK)**.
6. Was an acceptable case definition used in the study?	• **Yes (LOW RISK):** An acceptable case definition was used. • **No (HIGH RISK)**: An acceptable case definition was NOT used.	• For a study on low back pain, the following case definition was used: "Low back pain is defined as activity-limiting pain lasting more than one day in the area on the posterior aspect of the body from the bottom of the 12th rib to the lower gluteal folds." The answer is: **Yes (LOW RISK)**. • For a study on back pain, there was no description of the specific anatomical location 'back' referred to. The answer is: **No (HIGH RISK)**. • For a study on osteoarthritis, the following case definition was used: "Symptomatic osteoarthritis of the hip or knee, radiologically confirmed as Kellgren-Lawrence grade 2-4". The answer is: LOW RISK.
7. Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have **reliability and validity (if necessary)**?	• **Yes (LOW RISK):** The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re-test, piloting, validation in a previous study, etc. • **No (HIGH RISK)**: The study instrument had NOT been shown to have reliability or validity (if this was necessary).	• The authors used the COPCORD questionnaire, which had previously been validated. They also tested the inter-rater reliability of the questionnaire. The answer is: **Yes (LOW RISK)**. • The authors developed their own questionnaire and did not test this for validity or reliability. The answer is: **No (HIGH RISK)**.
8. Was the **same mode of data collection** used for all subjects?	• **Yes (LOW RISK):** The same mode of data collection was used for all subjects. • **No (HIGH RISK)**: The same mode of data collection was NOT used for all subjects.	The mode of data collection is the method used for collecting information from the subjects. The most common modes are face-to-face interviews, telephone interviews and self-administered questionnaires. Examples: • All eligible subjects had a face-to-face interview. The answer is: **Yes (LOW RISK)**. • Some subjects were interviewed over the telephone and some filled in postal questionnaires. The answer is: **No (HIGH RISK)**.
9. Was the **length of the shortest prevalence period** for the parameter of interest appropriate?	• **Yes (LOW RISK):** The shortest prevalence period for the parameter of interest was appropriate (e.g. point prevalence, one-week prevalence, one-year prevalence). • **No (HIGH RISK)**: The shortest prevalence period for the parameter of interest was not appropriate (e.g. lifetime prevalence)	The prevalence period is the period that the subject is asked about e.g. "Have you experienced low back pain over the previous year?" In this example, the prevalence period is one year. The longer the prevalence period, the greater the likelihood of the subject forgetting if they experienced the symptom of interest (e.g. low back pain). Examples: • Subjects were asked about pain over the past week. The answer is: **Yes (LOW RISK)**. • Subjects were only asked about pain over the past three years. The answer is: **No (HIGH RISK)**.
10. Were the **numerator(s) and denominator(s)** for the parameter of interest appropriate?	• **Yes (LOW RISK):** The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain). • **No (HIGH RISK)**: The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.	There may be errors in the calculation and/or reporting of the numerator and/or denominator. Examples: • There were no errors in the reporting of the numerator(s) AND denominator(s) for the prevalence of low back pain. The answer is: **Yes (LOW RISK)**. • In reporting the overall prevalence of low back pain (in both men and women), the authors accidentally used the population of women as the denominator rather than the combined population. The answer is: **No (HIGH RISK).**
***11.** Summary item on the overall risk of study bias*		
• **LOW RISK OF BIAS:** Further research is very unlikely to change our confidence in the estimate. • **MODERATE RISK OF BIAS:** Further research is likely to have an important impact on our confidence in the estimate and may change the estimate.		

- **HIGH RISK OF BIAS:** Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.

-

APPENDIX C

Researchers' contributions to the joint project

This project was run jointly with Kiri Clarke. Researcher contributions are set out below:

Aspects of study completed jointly

- All planning of study methodology.
- Liaison with ASD services via which recruitment took place.
- Writing the research project protocol.
- Writing the NHS REC application.
- Attending the NHS REC panel interview.

Aspects of study completed by Michele McKenner

- All liaison with mental health services other than IAPT via which recruitment of clinical comparison participants took place.
- Writing of NHS R&D application relevant to mental health services other than IAPT
- Writing of substantial amendment to NHS REC application relevant to recruitment of participants with psychosis
- Recruitment and interviewing of clinical comparison participants other than those recruited via IAPT (n=8) and interviewing of one IAPT participant.
- Recruitment of participants for the non-clinical control group (n=22).
- Analysis and write-up of data for ASD group versus clinical comparison group.

Aspects of study completed by Kiri Clarke

- All liaison with IAPT services via which recruitment of clinical comparison participants took place.
- Writing of NHS R&D applications relevant to the IAPT service and the ASD services.
- Recruitment and interviewing of participants from the IAPT service for the clinical comparison group (n=8 recruited, n=7 interviewed).
- Recruitment and interviewing participants from the ASD clinic (n=13).
- Recruitment of participants for the non-clinical control group (n=5).
- Analysis and write-up of data for ASD group versus non-clinical comparison group.

APPENDIX D

Letter of approval from National Research Ethics Service Committee

NHS
Health Research Authority

National Research Ethics Service

NRES Committee London - Bloomsbury
HRA NRES Centre Manchester
Barlow House 3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0161 625 7815
Fax: 0161 625 7299

16 July 2014

Dr Will Mandy
Research Department of Clinical, Educational and Health Psychology
University College London
1-19 Torrington Place
London
WC1E 7HB

Dear Dr Mandy

Study title:	**Validating the 3Di-sva: a short form diagnostic interview for autism spectrum disorders in adults**
REC reference:	**14/LO/1134**
IRAS project ID:	**145776**

Thank you for your email of 16 July 2014. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 09 July 2014.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Other [Schedule of Information Sheets, Consent Forms and Advertising Documents]		
Participant consent form [Parent - Non-clinical Controls]	V6.2	16 July 2014
Participant consent form [Parent - Affective Control Group]	V7.2	16 July 2014
Participant consent form [Parent - Psychosis Control Group]	V8.2	16 July 2014
Participant consent form [Parent - Pre 3Di]	V9.2	16 July 2014
Participant consent form [Parent - Post 3Di]	V10.2	16 July 2014
Participant consent form [Child - Affective Control Group]	V2.2	16 July 2014
Participant consent form [Child Psychosis Control Group]	V3.2	16 July 2014
Participant consent form [Child - Pre 3Di]	V4.2	16 July 2014
Participant consent form [Child - Post 3Di]	V5.2	16 July 2014
Participant consent form [Child - Non-clinical Controls]	V1.2	16 July 2014
Participant information sheet (PIS) [Parent - Non-clinical Controls]	V6.2	16 July 2014

Participant information sheet (PIS) [Parent - Affective Control Group]	V7.2	16 July 2014
Participant information sheet (PIS) [Parent - Psychosis Control Group]	V8.2	16 July 2014
Participant information sheet (PIS) [Parent - Pre 3Di]	V9.2	16 July 2014
Participant information sheet (PIS) [Parent - Post 3Di]	V10.2	16 July 2014
Participant information sheet (PIS) [Child - Non-clinical Controls]	V1.2	16 July 2014
Participant information sheet (PIS) [Child - Affective Control Group]	V2.2	16 July 2014
Participant information sheet (PIS) [Child Psychosis Control Group]	V3.2	16 July 2014
Participant information sheet (PIS) [Child - Pre 3Di]	V4.2	16 July 2014
Participant information sheet (PIS) [Child - Post 3Di]	V5.2	16 July 2014

Approved documents

The final list of approved documentation for the study is therefore as follows:

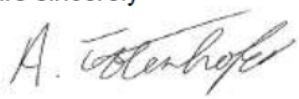
Document	*Version*	*Date*
Copies of advertisement materials for research participants [Affective control group flyer]	V1.1	12 March 2014
Copies of advertisement materials for research participants [Psychosis control group flyer]	V2.1	12 March 2014
Copies of advertisement materials for research participants [Psychosis control group poster]	V2.1	12 March 2014
Copies of advertisement materials for research participants [Affective control group poster]	V1.1	12 March 2014
Copies of advertisement materials for research participants [Non-clinical control group poster]	V3.1	12 March 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)	Arthur J Gallagher	26 July 2013
Letter from funder [Trainee indemnity & employment arrangements letter]		06 November 2009
Letter from sponsor	UCL	23 May 2014
Letters of invitation to participant [Invitation letter]	V1.1	26 March 2014
Non-validated questionnaire [3Di-sva]	V1	23 May 2014
Other	Michele McKenner CV	23 May 2014
Other [Schedule of Information Sheets, Consent Forms and Advertising Documents]		
Participant consent form [Child Psychosis Control Group]	V3.2	16 July 2014
Participant consent form [Parent - Post 3Di]	V10.2	16 July 2014
Participant consent form [Child - Pre 3Di]	V4.2	16 July 2014
Participant consent form [Child - Non-clinical Controls]	V1.2	16 July 2014
Participant consent form [Parent - Affective Control Group]	V7.2	16 July 2014
Participant consent form [Child - Post 3Di]	V5.2	16 July 2014
Participant consent form [Parent - Non-clinical Controls]	V6.2	16 July 2014
Participant consent form [Parent - Psychosis Control Group]	V8.2	16 July 2014
Participant consent form [Child - Affective Control Group]	V2.2	16 July 2014
Participant consent form [Parent - Pre 3Di]	V9.2	16 July 2014
Participant information sheet (PIS) [Child - Non-clinical Controls]	V1.2	16 July 2014
Participant information sheet (PIS) [Parent - Psychosis Control Group]	V8.2	16 July 2014
Participant information sheet (PIS) [Child - Affective Control Group]	V2.2	16 July 2014

Participant information sheet (PIS) [Parent - Pre 3Di]	V9.2	16 July 2014
Participant information sheet (PIS) [Parent - Post 3Di]	V10.2	16 July 2014
Participant information sheet (PIS) [Child - Pre 3Di]	V4.2	16 July 2014
Participant information sheet (PIS) [Child Psychosis Control Group]	V3.2	16 July 2014
Participant information sheet (PIS) [Child - Post 3Di]	V5.2	16 July 2014
Participant information sheet (PIS) [Parent - Non-clinical Controls]	V6.2	16 July 2014
Participant information sheet (PIS) [Parent - Affective Control Group]	V7.2	16 July 2014
REC Application Form	3.5	22 May 2014
Referee's report or other scientific critique report [Oliver Mason peer review]		03 October 2013
Research protocol or project proposal	V1	26 March 2014
Summary CV for Chief Investigator (CI)	Will Mandy	
Summary CV for student	Kiri Clarke	
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flow diagram]	V1	13 March 2014

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

14/LO/1134	**Please quote this number on all correspondence**

Yours sincerely



Dr Ashley Totenhofer
REC Manager

E-mail: nrescommittee.london-bloomsbury@nhs.net

Copy to: Dr Clara Kalu - University College London

Mrs Angela Williams – Noclor

Ms Michele McKenner - University College London

Ms Kiri Clarke - University College London

APPENDIX E

Sample information sheets

Camden and Islington NHS
NHS Foundation Trust

UCL

Validating the 3Di-sva: a diagnostic interview for autism spectrum disorders in adults

Participant Information Sheet

This sheet is for you to keep and tells you more about this study. Before you decide whether you would like to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and do not hesitate to ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

Some people with Autism Spectrum Disorders (ASD) reach adulthood without ever having had their condition recognised. This can prevent them from getting much needed support. We need more effective tools to help diagnose adults with suspected ASD, including tools which look at early childhood development and difficulties.

A relatively new tool for assessing ASD in adults is being used in the Asperger's Syndrome Diagnostic and Consultation Service in Camden which you are attending (the Service). This tool is called the Developmental, Diagnostic and Dimensional interview (or 3Di).

The 3Di involves interviewing a parent or relative of the person with suspected ASD to find out about their childhood development, as well as any current difficulties with social interaction and communication. There is already evidence that the interview is effective, but this study aims to investigate in greater detail how useful and effective it is.

What would I need to do?

The 3Di interview will be carried out with your parent(s) or relative as part of the routine assessment process with the Service. We would like your permission to use the information provided by your parent / relative in order to assess how effective the 3Di is. For example, we want to check that the 3Di is able to tell the difference between people who have ASD and those who do not.

Do I have to take part?

It is entirely up to you and your parent to decide whether or not to take part in this study. If you decide to take part, you are free to withdraw at any time, without giving a reason. **Please note that the clinical care you receive will not be affected in any way – whether or not you decide to take part in the study.**

What does the study involve?

The study will involve us accessing and using information provided by you and your parent as part of your routine assessment by the Service. This will include information given by your parent in the 3Di interview and information from some tasks and measures that you complete. All information will be kept strictly confidential, as explained in more detail below.

Is there anything that would stop me taking part?

If we are worried that you do not understand what the study involves, we will not include you in the study. However if, after you have taken part, something happens which means you no longer understand what the research involves, we may still use the information we have collected about you. All personal information will have been removed from the data and it will not be possible to identify you.

What are the possible disadvantages and risks of taking part?

We do not think there will be any disadvantages for you if you take part in the study. However, if you want to stop your participation for any reason, you are free to do so immediately.

Will my taking part in this study be kept confidential?

All data will be collected and stored in accordance with the Data Protection Act 1998. Only the researchers involved in the study will have access to data you or your parent provide(s) as part of this study. This information will be kept either in locked cabinets or on a secure and encrypted computer account, and will be stored anonymously at University College London (UCL). Any information you or your parent has provided will be kept strictly confidential. The only exception to this is if you mention something during the study which indicates that you may be a risk to yourself or others. In this case we would need to let someone relevant know, eg your GP. If this happens we will tell you.

What will happen to the results of the research?

The information will be analysed and compared with similar information provided by different groups of people who don't have ASD. These findings may be written up as reports, initially as part of a doctoral thesis at UCL. The results of the study may be presented at national and international conferences and published in academic journals. You will not be personally identified in any reports or publications of the research.

Who is organising and funding this research?

The project is funded by UCL. It is being conducted by the Research Department of Clinical, Educational and Health Psychology at UCL.

Contact for further information or assistance

If you have any further questions or would like assistance at any point during the study, please feel free to contact **Michele McKenner** or **Kiri Clarke** at UCL on 07989 085 846 or email adult.autism.study@gmail.com. In the case of a complaint, please contact Dr Will Mandy via w.mandy@ucl.ac.uk.

Thank you for reading this information

North East London NHS
NHS Foundation Trust

UCL

Validating the 3Di-sva: a diagnostic interview for autism spectrum disorders in adults

Participant Parent Information Sheet

This sheet is for you to keep and tells you more about this study. Before you decide whether you would like to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and do not hesitate to ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

Autism Spectrum Disorder (ASD) is a lifelong developmental disability which affects how a person communicates with and relates to other people and how they cope with change. We are researching ways of telling who has ASD and who does not have ASD.

We are looking for the parents of a group of people WITHOUT ASD to take part.

This study is investigating whether an interview called the 3Di can tell the difference between people with ASD and people who do not have ASD. The 3Di is a new tool for assessing ASD in adults. It involves interviewing the parents of the person with suspected ASD. The questions are about the person's childhood development, as well as any current difficulties with social interaction, communication and flexibility. There is already evidence that the 3Di is effective, this study aims to investigate in greater detail how useful and effective it is.

Why am I being asked to participate?

We are recruiting the parents of a group of people who have experienced psychosis to see if the 3Di can tell the difference this group from a group of people with ASD. This is important as sometimes symptoms of ASD can be confused with symptoms of psychosis. We are **not** asking you to take part because we believe your child might have ASD.

What would I need to do?

Once we have your consent and your child's consent, we will carry out the 3Di interview with you in person or over the phone, asking questions about your child's development. We would like to audio record the interview. It should take no more than 45-60 minutes. We will also meet with your child on one occasion for around 15 minutes. All information will be kept strictly confidential, as explained in more detail below.

Is there anything that would stop me taking part?

We will not be able to include you / your child in this study if there has ever been any concern that they may have ASD. This is because we are trying to see whether the 3Di can tell the

difference between a group of people who are known to have an ASD and groups of people who do not. If you do have concerns about your child having an ASD and wish to find out more then please discuss this with your GP. In addition, unfortunately, we will not be able to include you if either you or your child has difficulty understanding or speaking English.

If we are worried that you or your child does not understand what the study involves, we will not include you in the study. However if, after you have taken part, something happens which means you no longer understand what the research involves, we may still use the information we have collected about you. All personal information will have been removed from the data and it will not be possible to identify you.

Do I have to take part?

It is entirely up to you and your child to decide whether or not to take part in this study. If you decide to take part, you are free to withdraw at any time, without giving a reason. Please note that the clinical care your child receives will not be affected in any way – whether or not you decide to take part in the study.

Are there incentives for taking part?

To thank you for your time, once we have received all the relevant information you will receive a £10 Amazon voucher. You will also be entered into a prize draw to win a £50 Amazon voucher when the study is complete - you will have approximately a 1 in 60 chance of winning this voucher. Your child will also be entitled to a £10 Amazon voucher once they have taken part, and will be entered into a separate prize draw to win a £50 Amazon voucher.

What are the possible disadvantages and risks of taking part?

We do not think there will be any disadvantages for you if you take part in the study. If you want to stop your participation for any reason, you are free to do so immediately.

Will my taking part in this study be kept confidential?

All data will be collected and stored in accordance with the Data Protection Act 1998. Only the researchers involved in the study will have access to data you or your child provide(s) as part of this study. This information will be kept either in locked cabinets or on a secure and encrypted computer account, and will be stored anonymously at University College London (UCL). Any information you or your child has provided will be kept strictly confidential. The only exception to this is if you mention something during the study which indicates that you may be a risk to yourself or others. In this case we would need to let someone relevant know, eg your GP. If this happens we will tell you.

What will happen to the results of the research?

The information will be analysed and compared with similar information provided by groups of people who have ASD, or who have other mental health difficulties, or who don't have ASD or mental health difficulties. These findings may be written up as reports, initially as part of a doctoral thesis at UCL. The results of the study may be presented at national and international conferences and published in academic journals. You will not be personally identified in any of these reports or publications.

Who is organising and funding this research?

The project is funded by UCL. It is being conducted by the Research Department of Clinical, Educational and Health Psychology at UCL.

Contact for further information or assistance

If you have any further questions or would like assistance at any point during the study, please contact **Michele McKenner** or **Kiri Clarke** at UCL on 07989 085 846 or email adult.autism.study@gmail.com. In the case of a complaint, please contact Dr Will Mandy via w.mandy@ucl.ac.uk.

Thank you for reading this information

APPENDIX F

Sample consent forms

Camden and Islington NHS
NHS Foundation Trust

UCL

CONSENT FORM (Version 4.2)

Title of Project: Validating the 3Di-sva: a diagnostic interview for autism spectrum disorders in adults

	Yes/No*
I confirm that I have read and understand the information sheet dated 16/07/2014 (version 4.2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	YES / NO
I understand that agreeing for my data to be used for this research is voluntary and that I am free to withdraw it at any time, without giving any reason, and without my health care or legal rights being affected.	YES / NO
I understand that all personal data relating to participants is anonymised and held and processed in the strictest confidence when used for the purposes of this study.	YES / NO
I understand that researchers will not have access to any of my NHS records other than the data from my clinic assessment required for this study.	YES / NO
I understand that relevant sections of my data collected during the study may be looked at by individuals from University College London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	YES / NO
I agree for data from my clinic assessment to be included in this study.	YES / NO

* delete as appropriate

Participant

…… …… …… ……

First name Last name Date Signature

Person taking consent

…… …… ……

Name Date Signature

(1 copy for participant; 1 copy for researcher)

Names of researchers:
Dr Will Mandy, University College London
Dr Jason Crabtree, University College London
Michèle McKenner, University College London
Kiri Clarke, University College London

North East London NHS
NHS Foundation Trust

UCL

CONSENT FORM (Version 8.2)

Title of Project: Validating the 3Di-sva: a diagnostic interview for autism spectrum disorders in adults

	Yes/No*
I confirm that I have read and understand the information sheet dated 16/07/2014 (version 8.2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	YES / NO
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected or my child's health care being affected.	YES / NO
I understand that all personal information I give regarding my child is anonymised and held and processed in the strictest confidence.	YES / NO
I understand that researchers will not have access to mine or my child's NHS records.	YES / NO
I understand that relevant sections of my data collected during the study may be looked at by individuals from University College London, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	YES / NO
I agree for my interview to audio recorded.	YES / NO
I agree to take part in this study.	YES / NO

* delete as appropriate

Participant

....

First name Last name Date Signature

Person taking consent

....

Name Date Signature

(1 copy for participant; 1 copy for researcher)

Names of researchers:
Dr Will Mandy, University College London
Dr Jason Crabtree, University College London
Michèle McKenner, University College London
Kiri Clarke, University College London

APPENDIX G

Invitation letter sent to ASD research database participants

Camden and Islington NHS
NHS Foundation Trust

UCL

Dear xxxxxx

Re: Research project into diagnostic interview for Autism Spectrum Disorders (ASD)

When you visited the Asperger's Syndrome Diagnostic and Consultation Service (ASDCS), you indicated that you were happy for anonymised information about you to be stored on the confidential ASDCS database, solely for the purpose of audits and research. You also agreed to be added to our Autism and Asperger Research Register, a register of individuals who are willing to be contacted about opportunities to participate in new research projects into Asperger's Syndrome and other Autism Spectrum Conditions.

New research project
We are contacting you about a new research project which is investigating an interview used for diagnosing ASD in adults. The interview is called the 3DI (the Developmental, Diagnostic and Dimensional Interview). The 3DI helps us gather information about a person's childhood development as well as current difficulties with social interaction and communication.

When you visited the Clinic, a family member, or someone else who knows you well, completed the 3DI as part of your assessment. This data has been stored, in an anonymised form, on the ASDCS database.

There is already evidence that the 3DI is effective. Our research aims to investigate in greater detail how useful and effective it is. We want to show how well the interview can distinguish between people who have ASD and people who don't. This is really important for improving diagnostic services for other adults with suspected ASD.

You already have my 3DI, so what do you want me to do now?
In order to be able to use your data in our research project we would need to collect a bit more information from you. We are writing to ask if you would be willing to complete an additional brief task – which simply involves reading out a list of words – to help us with our research.

This information will help us ensure that the abilities of the people we use from the Asperger's Clinic are similar to those of other people taking part who do not have ASD.

The task should take no more than 5-10 minutes. It could be done by meeting in person on one occasion or, if you have access to an email account on a computer, it could be done over the phone.

Names of researchers:
Dr Will Mandy & Dr Jason Crabtree, University College London
Michèle McKenner & Kiri Clarke, University College London

Why should I help?

Some people with Autism Spectrum Disorders reach adulthood without ever having had their condition recognised. This can prevent them from getting much needed support.

Whilst there is a lot of research looking at how to diagnose children with suspected ASD, we need more research showing us the best ways to diagnose adults.

By taking 10 minutes to provide us with this extra bit of information you will help us to develop user-friendly and effective ways of diagnosing ASD in adults.

What should I do now?

- Please contact us on 07989 085 846 (you may call or text) or email us at adult.autism.study@gmail.com to let us know if you are interested in taking part.

- *Please also let us know if you are not interested in participating so that we can remove you from our database.*

Registering your interest does not mean you have agreed to provide the additional data requested. You will be given further, more detailed information about the study before consenting to take part.

Please note that if we do not hear from you regarding whether you would like to take part or not within two weeks of sending this letter, we will attempt to contact you by phone to follow up this invite. If we cannot get through to you after two attempts at calling we will not try again and will assume you do not wish to take part.

Yours sincerely,

KLClarke

Kiri Clarke & Michele McKenner
Trainee Clinical Psychologists
University College London

In collaboration with Dr Andre Strydom and Dr Bano Hassan, Asperger's Syndrome Diagnostic and Consultation Service.

APPENDIX H

Invitation letter sent to individuals on the IAPT database

INVITATION TO TAKE PART IN CLINICAL RESEARCH

Dear [insert participants name],

When you recently visited Camden Psychological Therapies you agreed to consider taking part in research studies being carried out at the service. We are currently recruiting participants from this service and would like to invite you to take part.

As a reward for taking part all participants will receive a £5 voucher and be entered into a prize draw to win a £50 voucher.

What is the research?

The research is investigating a diagnostic interview for adults with Autism Spectrum Disorders (ASD).

We are looking for people WITHOUT autism to take part in our study.

We want to make sure that the interview, called the 3Di, can tell the difference between people known to have ASD and people who do not have ASD.

Sometimes ASD can be confused with other symptoms, such as those of anxiety or mood disorders. We need to make sure that the 3Di is capable of telling the difference between someone who has experienced anxiety or mood difficulties and someone who has ASD. This is why we are recruiting individuals from Camden Psychological Therapies who have experienced anxiety or mood difficulties.
Again, we are **not** asking you to take part because we believe you might have an ASD.

What would I need to do?
If you decide to take part, we will meet with you on one occasion. The meeting will take about 15 minutes. We will ask you to complete two brief measures of anxiety and depression, and complete one brief task involving reading out some words.

We would also need you to ask a parent (or someone else, such as a relative, who knew you well growing up) for permission for us to contact them so that they can take part in the research too. The 3Di involves interviewing someone who has known you since early childhood about your childhood development. This is because the symptoms of ASD first appear in early childhood so it is important for us to find out about your first years of life. If your parent agrees we would contact them and do a interview with them over the phone. The interview will take around 45 minutes. Once we have everything we need, you and your parent will both receive a £5 voucher.

Names of researchers:
Dr Will Mandy & Dr Jason Crabtree, University College London
Michèle McKenner & Kiri Clarke, University College London

Is there anything that would stop me taking part?
We will exclude anyone from the study who has any concerns that they themselves may have an autism spectrum disorder. Should you have concerns about having an ASD and wish to find out more then please see your GP. We also cannot include anyone who has difficulty understanding or speaking English, and anyone who does not have a parent or relative who is willing to take part.

Please contact us on 07989 085 846 to let us know if you are interested in taking part (or if you want to let us know that you are not interested in participating). You may either call or text the number. You may also email us at adult.autism.study@gmail.com. Registering your interest does not mean you have agreed to take part. You will be given further, more detailed information about the study before consenting to take part.

Please note that if we do not hear from you regarding whether you would like to take part or not within two weeks of sending this letter, we will attempt to contact you by phone to follow up this invite. If we cannot get through to you after two attempts at calling we will not try again and will assume you do not wish to take part.

Yours sincerely,

Kiri Clarke
Trainee Clinical Psychologist, University College London