

**Autistic traits below the clinical threshold: re-examining the
Broader Autism Phenotype in the 21st Century**

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Abstract

Diagnosis, intervention and support for people with autism can be assisted by research into the aetiology of the condition. Twin and family studies indicate that autism spectrum conditions are highly heritable; genetic relatives of people with autism often show milder expression of traits characteristic for autism, referred to as the Broader Autism Phenotype (BAP). In the past decade, advances in the biological and behavioural sciences have facilitated a more thorough examination of the BAP from multiple levels of analysis. Here, the candidate phenotypic traits delineating the BAP are summarised, including key findings from neuroimaging studies examining the neural substrates of the BAP. We conclude by reviewing the value of further research into the BAP, with an emphasis on deriving heritable endophenotypes which will reliably index autism susceptibility and offer neurodevelopmental mechanisms that bridge the gap between genes and a clinical autism diagnosis.

Keywords: autism, broader autism phenotype, social cognition, phenotypic heterogeneity, endophenotypes

Introduction

Conditions on the autism spectrum* refer to a set of neurodevelopmental conditions that are characterised by impairments in social interaction and communication, and by an atypically restrictive and repetitive repertoire of interests and activities (DSM-IV, ICD-10). Early twin studies of autistic disorder, commencing in 1977 by Folstein and Rutter, and later twin studies using contemporary diagnostic criteria, indicate that autism has a significant genetic component with a heritability estimate exceeding 80% (Ronald and Hoekstra, in press). Apart from twin studies, family studies provide clues implicating the importance of genetic influences on autism. The 'Broader Autism Phenotype' (BAP) is a term describing a group of 'sub-threshold' social skills and communication traits and unusual personality features that are frequently found in the relatives of people with autism and which are believed to be milder manifestations of traits characteristic for clinically diagnosed autism (Constantino et al. 2006, Rutter 2000). The BAP concept derives from observations made in the 1940s by Leo Kanner and Hans Asperger, who reported behavioural features in parents that were similar in kind to those of their autistic offspring. For example, in Kanner's case studies of children with 'autistic psychopathy' in 1943, both first and second-degree relatives were selectively described as late speakers, mildly obsessive and uninterested in people (Kanner 1943). Likewise, Asperger described a subset of parents of children with autism as withdrawn, pedantic, eccentric and loners who had problems relating to the outside world (Asperger, translated by Frith 1991). Thus from a very early period, observations suggested that the expression of

* in this review, the term 'autism' is commensurate with 'autism spectrum condition' and includes the sub-categories: autistic disorder, Asperger syndrome and Pervasive development disorder not otherwise specified (DSM-IV).

autistic traits extends beyond the clinical boundaries of autism to include a mild sub-threshold expression in relatives, supporting the hypothesis that the aetiology of autism has a significant genetic component.

It has been over 12 years since the BAP was first comprehensively reviewed (Bailey et al. 1998). In over a decade since this review was written, there have been substantial advances in the methodological tools used by researchers to study the BAP. In the last 10 years, various researchers (e.g. Baron-Cohen et al. 2001b, Constantino et al. 2006, Hoekstra et al. 2008) advanced the notion that, rather than a discrete category, the autism phenotype can be conceptualised as a set of continuous, quantitative traits that merge into the general population. This has been accompanied by the development of new psychometric scales, such as the Autism-Spectrum Quotient (Baron-Cohen et al. 2001b) and the Social Responsiveness Scale (Constantino 2002) which have allowed sub-threshold autistic traits to be measured more precisely. The last decade has also seen a wider availability of brain scanning techniques, which have allowed the structure and function of the brain to be examined more directly in individuals diagnosed with autism, their relatives and control groups. The results and conclusions of brain scanning experiments are also beginning to dramatically improve our understanding of the neural underpinnings of the BAP. This review therefore provides an up-to-date summary of research findings on the BAP in the fields of psychology, cognitive neuroscience and related disciplines.

Measuring and defining the BAP: methodological considerations

In 1977, Folstein and Rutter's pioneering study of concordance for autism in monozygotic (MZ) and dizygotic (DZ) twins provided a pattern of findings consistent with a broader phenotype for autism (Folstein and Rutter, 1977). Since then, researchers have explored the BAP using a variety of measures and research designs. Before setting out the research findings of the different studies, it is important to highlight some key differences in the methods used. Firstly, several early family studies supporting the presence of a broader phenotype in the parents and/ or siblings of autistic probands were heavily reliant on qualitative, categorical data collected from observational reports and interviews (e.g. Bolton et al. 1994, Gillberg 1989, Landa et al. 1992, Piven et al. 1994, Piven and Palmer 1997, Wolff et al. 1988). These studies used a discrete measure of the BAP; similar to a discrete autism diagnosis, the BAP was either present or absent. With the development of scales such as the Autism-Spectrum Quotient and the Social Responsiveness Scale, the characteristics of the BAP can now be assessed quantitatively.

As well as a shift from dichotomous to quantitative measures, methodology has differed in terms of which participants are included in studies on the BAP. Most studies focus on relatives of people with autism who do not have a clinical autism diagnosis themselves. As such, they are clinically 'unaffected' with autism. However, not all studies have excluded affected relatives (e.g. Virkud et al. 2009), making it difficult to evaluate whether average elevated autistic traits can simply be ascribed to this clinical subgroup of the sample (see Hoekstra and Wheelwright 2010 for discussion). Some studies analyse the BAP in the infant siblings of children diagnosed with autism. For example, Holmboe

et al. (2010) explored attentional disengagement and selective inhibition problems in infant siblings of autistic probands. Other studies focusing on ‘at-risk’ infant siblings include Cassel et al. (2007), Merin et al. (2007), Presmanes et al. (2007) and Toth et al. (2007) (see Table 1 on pages 96-98, which summarises a range of research studies examining autistic traits in the infant siblings of autistic probands). Whilst components of the autism phenotype can be found in this experimental group, it is not clear whether these are features of the BAP or early indicators of the full autism phenotype, since a reliable autism diagnosis can not be given yet. Whether these children are truly ‘unaffected’ with clinical autism and display early sub-threshold expression of autistic traits or are children who may later receive an autism spectrum diagnosis is thus uncertain using this methodological design. Other researchers in turn have used more liberal participant selection criteria, choosing to examine autistic traits in the general population rather than in relatives of people with autism (e.g. Jobe and White 2007).^{*} Still other researchers have extremely conservative selection criteria, splitting up the genetic relatives of autistic probands into ‘BAP+’ and ‘BAP-’ groups following one or more discrete criteria, and measuring autistic traits in the ‘BAP+’ group only (e.g. Adolphs et al. 2008, Losh et al. 2009) rather than analysing average differences amongst all genetic relatives taken together (e.g. Dalton et al. 2007).

In addition, studies compare the relatives of autistic probands with different types of control groups. Some researchers have used a clinical control group, such as parents of children with Down Syndrome (e.g. Piven et al. 1997b, Ruser et al. 2007) or Specific

^{*} in this review we restrict the discussion of the BAP to studies conducted in the relatives of people with autism.

Language Impairment (e.g. Lindgren et al. 2009) which helps to eliminate confounding variables associated with caring for a child with special needs. In contrast, some research studies use a non-clinical control group; the genetic relatives of typically developing individuals who do not have any psychiatric conditions (e.g. Losh et al. 2009). In some studies these comparison groups have been well-matched on variables such as age, sex and IQ (e.g. Dorris et al. 2004, Wong et al. 2006) but less so in others (e.g. Piven and Palmer 1997).

It is important to bear these methodological differences in mind when reading the findings presented in this review. Since Folstein and Rutter's landmark twin study in the 1970s, there have been a number of family and twin studies looking for autism-related characteristics in the relatives of probands, which have achieved mixed success. Here, these candidate traits are examined at different levels of analysis, starting with the behavioural (including the 'three domains of impairment' (DSM-IV) defining the narrower phenotype of autism). This level is assessed using interviews, observational assessments and self/ other-report questionnaires, which explore the expression of autistic traits in naturalistic contexts. The review then examines the BAP from the cognitive level (e.g. atypical social cognition, executive function and visual attention) using performance-based measures that systematically examine brain functioning in experimentally controlled settings. Finally this review summarises neuroimaging studies investigating possible neuroanatomical and neurofunctional correlates of the BAP. The overview that follows comes with the caveat that there is strong overlap between the 'behavioural' and 'cognitive' levels to the extent that some behavioural measures

described could also be considered cognitive and vice-versa. Furthermore, within the ‘behavioural’ level of impairments there is strong overlap between the domains of ‘reciprocal social interaction’ and ‘language and communication’. Therefore some traits that are here included in the domain of ‘reciprocal social interaction’ may also be included in the domain of ‘language and communication’ and vice-versa.

The candidate traits that are examined also depend on the stage of development that the participants are sampled. For example, a number of studies have examined early social behaviours such as joint attention, requesting, eye gaze movements and play behaviour in the younger infant siblings of children with autism (e.g. Landa et al. 2007, Merin et al. 2007, Toth et al. 2007). Other studies have focused on later social behaviour in older relatives of people with autism, such as empathic understanding, social expressiveness and social motivation (e.g. Szatmari et al. 2008, Dawson et al. 2007). Isolated traits appearing early in human development may serve as important precursors for the emergence of traits at a later stage in development. Therefore a distinction is made here between an ‘early’ BAP arising in the ‘at-risk’ infant siblings of children with autism and a ‘later’ BAP present in the older relatives of people with autism. To aid the reader in the following sections, a summary of the traits discussed in the early and later BAP has been provided in Tables 1 and 2 respectively (see pages 96-102).

Behavioural level

Language and communication

Characteristics pertaining to the language domain of autistic atypicalities have been extensively studied in the relatives of people with autism. Research findings suggest that parents and siblings of autistic probands have significantly greater difficulty using language to communicate for social purposes (pragmatics) compared to controls (see Tables 1 and 2). For example, the infant siblings of children with autism identified with the BAP using the scores of items taken from the Autism Diagnostic Observation Schedule (Lord et al. 2002) scored poorly on semantic-pragmatic language compared to typically developing infants (Ben-Yizhak et al. 2011). Pragmatic difficulties have also been found in adult relatives e.g. the parents of children with autism scored poorly on the ‘pragmatic skills’ subscale of a self-report questionnaire called the ‘Communication Checklist-Adult Version’ (Whitehouse and Bishop, 2009) compared to controls from the general population. However, this group difference did not reach statistical significance (Whitehouse et al. 2010). Similarly, the parents of autistic probands categorised as ‘aloof’ tended to have greater problems with pragmatic language use, as indicated by an interview-based performance measure called the Pragmatic Rating Scale (Landa et al. 1992; Losh and Piven 2007). Studies by Bishop et al. (2004) and Whitehouse et al. (2007) assessed the language abilities of parents of children with autism and found significantly higher average levels of pragmatic difficulties compared to both clinical and non-clinical control groups, as indicated by the communication and social subscales of the Autism-Spectrum Quotient. An additional study conducted by the same research group found associations between the same two combined subscales of the Autism-Spectrum Quotient in fathers and children scoring low on the Children’s Communication Checklist-2 (Bishop 2003; Bishop et al. 2006). Similar findings have also been reported

using large sample sizes by Wheelwright et al. (2010) and in a cross-cultural validation study of the BAP using clinical and non-clinical samples from Italy (Ruta et al., in press). In both studies, the parents of children with autism scored significantly higher than a control group for difficulties on the communication subscale of the Autism-Spectrum Quotient.

Other family studies examining the communication domain used a modified version of the Pragmatic Rating Scale; both Piven et al. (1997b) and Ruser et al. (2007) found that the parents of probands with autism had significantly lower scores on this measure than a clinical control group (parents of Down Syndrome children). This was especially true for the male relatives of autistic probands who displayed poor social-pragmatic abilities, as measured by the modified Pragmatic Rating Scale. However, the lower communication abilities found were not specific to autism but also found in the relatives of probands with specific language impairment, indicating overlap in symptomatology and potentially genetic aetiology (Ruser et al. 2007). Other studies finding significantly higher frequencies of communication/ pragmatic abnormalities in the biological relatives of autistic probands include Bolton et al. (1994) and Szatmari et al. (2000), using the Autism Family History Interview (Bolton et al. 1994), and Hurley et al. (2007) using a measure designed to detect the BAP in parents of children with autism (the Broad Autism Phenotype Questionnaire; Hurley et al. 2007). Therefore, difficulties in the social use of language could be a reliable feature of the BAP. However, not all studies have found clear differences in the language and communication abilities of autism relatives compared to clinical and typically developing controls. For instance, Pilowsky et al.

(2003) found no differences in language difficulties (including scores on the Pragmatic Rating Scale) between siblings of children with autism and two clinical control groups; the siblings of children with developmental language disorder and the siblings of children with learning difficulties. Similarly, Folstein et al. (1999) found no differences in language-related difficulties between the siblings of autistic probands and Down Syndrome probands, using the Autism Family History Interview. The researchers found a difference in Pragmatic Rating Scale scores only when family members were split up into those with and without early language-related cognitive difficulties (as reported retrospectively by the parents).

Autism symptomatology in the language and communication domain of impairment can also include a significant delay in the acquisition, comprehension and articulation of speech. Subsets of autistic probands never acquire fluent speech, whilst others can speak spontaneously but have problems with the structural aspects of language (Tager-Flusberg and Joseph 2003). It is not clear whether these difficulties are consistently found in the relatives of autistic probands. Language delay was reported in 22% of siblings of autistic probands between 2 and 6 years of age in a study by Chuthapisith et al. (2007) and 20% of siblings of children with autism in a study by Constantino et al. (2010), half of which were also considered to exhibit 'autistic speech'. Likewise, delayed language development was reported in a longitudinal study of younger siblings of children with autism, aged 5 to 18 months (Iverson and Wozniak, 2007). Videotapes of autism-siblings at home with their caregivers revealed delays on communicative milestones including reduplicated babble and first words, as well as delays in language comprehension and

expression. This was coupled with delays in the siblings' motor development (e.g. less time spent in different postures) suggesting a possible relationship between the early disruption of the motor and vocal systems during development which could play a causal role in autism and the BAP. However, Iverson and Wozniak did not measure the siblings' general cognitive development so it is not clear whether they were showing signs of general developmental delay or specific delays characteristic of autism and the BAP. Likewise, Stone et al. (2007) also reported poorer scores on a parental measure of language and communication called the MacArthur Communicative Development Inventories (Fenson et al. 1993) in the infant siblings of children with autism versus a sample of typically developing children.

Other studies have examined language difficulties in older siblings of autistic probands. For instance Folstein and Rutter's seminal studies in 1977 found high concordance rates in MZ twin pairs (relative to DZ twin pairs) for broader autistic-related traits including articulation disorder and retrospective reports of language delay; 9 out of 11 non-autistic children in MZ pairs had cognitive/ language difficulties (82% concordance) compared to 1 out of 10 non-autistic children in DZ pairs (10% concordance). Support for the presence of similar characteristics in the relatives of autistic probands has also been described by Bolton et al. (1994) who reported broad language and communication deficits using the Autism Family History Interview, including delays in the onset of speech and articulation difficulties. Bolton and colleagues also found a marked increase in the reporting of reading and spelling problems. Likewise in a study by Folstein et al. (1999), significantly more parents of children with autism reported language-related

difficulties including reading and spelling compared to parents of Down Syndrome children, although this was not found for siblings of autistic probands. When reading and spelling performance has been assessed in autism relatives, differences in test scores have not been consistently found compared to control groups (e.g. Pilowsky et al. 2007, Schmidt et al. 2008; see 'language ability' section). Finally Landa et al. (1991) found significant differences between parents of autistic probands and parents of Down Syndrome probands on a measure of spontaneous narrative discourse. Overall, the current consensus indicates that language delay, social-pragmatic problems and spontaneous narrative discourse could be potential components of the BAP, with moderate support for both the structural components of language and reading, spelling and articulation difficulties.

Reciprocal Social Interaction

Significant impairment in reciprocal social interaction is a defining clinical feature of autism and the literature currently suggests that a milder version of these behavioural impairments extends to the relatives of autistic probands. A large number of recent studies have examined social behavioural deficits in the at-risk infant siblings of children with an autism diagnosis. For example, at-risk siblings are less likely to respond to their name on the first or second call compared to typically developing children at 12 months of age (Nadig et al. 2007). Infant siblings of autistic probands have also been reported to initiate joint attention significantly less frequently than a typically developing control group (e.g. Cassel et al. 2007, Goldberg et al. 2005, Landa et al. 2007). Similarly, siblings

are less able at *responding* to joint attention compared to typically developing controls (Presmanes et al. 2007; but see Goldberg et al. 2005 for negative findings using a less sensitive measure of joint attention). Siblings later classified as ‘BAP+’ also displayed deficits responding to joint attention compared to siblings later classified as ‘BAP-’ (Sullivan et al. 2007). Other social behavioural deficits detected in at-risk siblings include reduced frequency of requesting behaviours (Goldberg et al. 2005, Cassel et al. 2007), reduced response to social interaction (Goldberg et al. 2005) and differences in eye gaze movements; for example, shifting gaze to and from the caregiver less frequently (Ibanez et al. 2008), gazing away from the caregiver for longer periods (Ibanez et al. 2008), gazing less at the caregiver’s eyes relative to the mouth (Merin et al. 2007) and looking less at the caregiver and more at a novel object during a social-object learning task (Bhat et al. 2010). However, it is important to note that in a number of these studies there was no longitudinal follow-up to determine whether the infants that performed poorly on these tasks would express BAP traits later in development (e.g. Bhat et al. 2010, Goldberg et al. 2005, Merin et al. 2007, Nadig et al. 2007, Presmanes et al. 2007, Cassel et al. 2007). Instead the infants examined in these studies may later display the full autism phenotype. Other studies have circumvented this problem by later classifying siblings into ‘BAP+’, ‘BAP-’ and ‘ASD’ groups (e.g. Landa et al. 2007 and Sullivan et al. 2007).

A small number of studies have examined socioemotional behaviour in at-risk autism siblings during play with their caregivers. Using a paradigm called the ‘face-to-face/ still face’ (FFSF) task (Tronick et al. 1978), caregivers play with their child and are then

asked to hold a still, expressionless face for a sustained period to increase negative emotion (cry-faces) and reduce positive emotion (smiling) in the infant, before the caregiver resumes play. Cassel et al. (2007) carried out a longitudinal study examining changes in positive and negative emotion generated by the FFSF task in infants at a low risk and high risk for autism. They found that at 6 months, the siblings of children with autism smiled significantly less during the FFSF task than low-risk, typically developing infants. Likewise, Yirmiya et al. (2006) reported that infant siblings of children with autism got less upset and displayed more neutral affect during the still face procedure of the FFSF task. Those siblings that displayed higher rates of neutral affect during the still face procedure initiated fewer joint attention bids and requesting behaviours at 14 months. Also, mother-infant synchrony was poorer for infant-led interactions during free play in the autism-sibling group, compared to typically developing infant controls. The FFSF task has also been used to investigate eye gazing/ visual attention, with various studies reporting differences in eye gaze movements towards the caregiver and inanimate objects between at-risk siblings and low-risk, typically developing controls (e.g. Ibanez et al. 2008, Bhat et al. 2010, Merin et al. 2007) These studies suggest that differences in eye gaze movements could be an early indicator of the BAP.

Other studies looking at the early social BAP include Toth et al. (2007) and Christensen et al. (2010) who examined play behaviour in at-risk siblings. Using the Communication and Symbolic Behavior Scale-Developmental Profile (Wetherby and Prizant 2002), Toth et al. reported that infant siblings of children with autism displayed less symbolic behaviour as well as fewer responsive social smiles and distal gestures such as pointing

during social interactions. In contrast, using their own assessment of play behaviour, Christensen et al. reported no differences in the rates of symbolic play actions between a sample of at-risk siblings and typically developing infant controls at 18 months, although at-risk siblings showed significantly more non-functional repeated play behaviours than controls (see 'repetitive, stereotyped behaviours and interests' section).

A number of studies have suggested that difficulties in this domain extend to the adult relatives of autistic probands. Using a structured clinical interview, Wolff et al. (1988) reported that the parents of children with autism displayed a greater lack of rapport and higher 'social gaucheness' compared to the parents of children with special needs (excluding autism), whilst Gillberg (1989) found some qualitative evidence of mild social deficits in the parents of probands with Asperger Syndrome, based on interviews about family psychiatric history. Likewise, using a semi-structured interview, Narayan et al. (1990) described some parents of children with autism as displaying social gaucheness. High rates of broadly defined social difficulties in first-degree relatives have also been reported by Bolton et al. (1994) and occasionally in second-degree relatives (grandparents, aunts and uncles) using the Autism Family History Interview (Piven et al. 1997a), which suggests that these problems could have a strong genetic liability. More recently, Szatmari et al. (2008) have suggested that alexithymia could be an important feature of the BAP: that is, a difficulty in identifying, describing and processing one's own emotions. Parents of children with autism scored higher than a clinical control group (the parents of children with Prader Willi Syndrome) on a self report questionnaire called the Toronto Alexithymia Scale (Bagby et al. 1994), especially on the subscale: 'difficulty

identifying feelings'. In fathers, high alexithymia scores were associated with high levels of repetitive behavioural symptoms in their children with autism, as measured using the Autism Diagnostic Interview-Revised (Lord et al. 1994).

Compared to both clinical and non-clinical control groups, the parents of children with autism have been reported as having lower quality or quantity of friendships and a preference for less social activities and behaviours (e.g. Briskman et al. 2001, Losh and Piven 2007, Losh et al. 2008, Piven et al. 1997a, Santangelo and Folstein 1995). Some studies indicate gender differences in the degree of social impairment e.g. using the Autism Family History Interview, Piven et al. (1997a) reported that 57% of fathers of children with autism had broadly defined social deficits compared to 13% of fathers of children with Down syndrome. This contrasted with 36% and 13% of mothers with autism and Down syndrome respectively, suggesting that social impairments may be especially prevalent in male relatives of individuals with autism. Similarly, using a new interview-based measure called the Broader Phenotype Autism Symptom Scale (Dawson et al. 2007), fathers of children with autism scored significantly higher than mothers on 2 domains including 'social expressiveness' (Dawson et al. 2007). Sex differences were also reported in a study by Virkud et al. (2009) who found significantly higher aggregations of autistic traits in the brothers of children with autism using the Social Responsiveness Scale. However, rather than concentrating on unaffected relatives only, Virkud et al. included siblings with autism diagnoses in their analyses which elevated mean scores on this measure (see Hoekstra and Wheelwright 2010). Future analyses of the BAP conducted by the same research group were modified to include unaffected

relatives only, producing similar results: there was an aggregation of autistic traits in the unaffected relatives of siblings, especially brothers from multiple-incidence autism families (Constantino et al. 2010). This supported previous work carried out by the same research group reporting significantly reduced social responsiveness in the siblings of autistic probands compared to a clinical control group (Constantino et al. 2006). Research studies have also reported elevated scores on the ‘social skills’ subscale of the Autism-Spectrum Quotient in the parents of children with autism compared to parents of typically developing children; this was especially true for fathers (Wheelwright et al. 2010, Ruta et al., in press). Likewise, using the Communication Checklist-Adult Version, parents of children with autism reported significantly higher scores on the subscale ‘social engagement’ (i.e. indicating greater deficits) compared to a large sample of typical adults from the general population (Whitehouse et al. 2010). Altogether, these studies indicate significant impairments in reciprocal social interaction amongst the relatives of autistic probands, particularly fathers and brothers, and provide evidence to warrant the inclusion of these behavioural traits in the BAP.

Repetitive, Stereotyped Behaviour and Interests

The third domain of symptoms characterising clinical diagnoses of autism involve restricted, repetitive and stereotyped patterns of behaviour, interests and activities (DSM-IV). To date, a modest number of studies have suggested that the relatives of autistic probands display a milder version of these clinical manifestations. In a study on infant siblings of children with autism, Christensen et al. (2010) reported significantly higher

frequency of non-functional repeated play behaviours compared to typically developing infants. In a study involving older relatives, Smith et al. (2009) carried out a factor analysis on the restricted, repetitive behaviours and interests (RRBI) domain of autism using the Autism Diagnostic Interview-Revised and examined associations between RRBI and personality traits linked to autism in the parents. They found that the factor 'intense preoccupations' in affected children correlated significantly with the personality traits 'rigid' and 'aloof' in fathers, suggesting that there may be a genetic association between these traits. The parents of children with autism have also been reported as rigid/perfectionistic in a small number of other studies (e.g. Losh et al. 2008, Piven et al. 1997b; see 'personality traits' section). Wolff et al. (1988) interviewed parents of autistic probands and non-autistic children with special needs and found parents, and especially fathers, of children with autism to exhibit special interest patterns (corresponding with the restrictive behaviours commonly found in autistic probands). However, this trait failed to distinguish parents of children with autism from parents of non-autistic children with special needs. Likewise, Narayan et al. (1990) interviewed 21 parents of children with autism and reported a significant tendency for parents to display a 'single-minded pursuit of special, often intellectual, interests'. Bolton et al. (1994) found elevated rates of stereotyped behaviours in first-degree relatives of autistic probands compared to the relatives of Down Syndrome probands, whilst Piven et al. (1997a) reported similar findings in first and second-degree relatives of autistic probands, using the Autism Family History Interview; 26% of autism fathers had stereotyped behaviours compared to 3% of Down Syndrome fathers whilst 12% of autism mothers had stereotyped behaviours versus 0% of Down Syndrome mothers. Finally, parents of children with autism were

reported to score significantly higher than a clinical and non-clinical control group on an experimental questionnaire designed to tap into real-life non-social skills and preferences (e.g. insistence on routines and circumscribed hobbies; Briskman et al. 2001).

Overall, the small numbers of studies that have examined restrictive repetitive behaviours in first degree relatives of autistic probands have found some evidence of a BAP in this domain. This includes broadly defined stereotyped behaviours using the Autism Family History Interview, reports of real-life non-social skills and preferences and a rigid/ 'perfectionistic' personality. The studies that have so far examined this behavioural domain in autism relatives have largely relied on categorical data. Future work should investigate repetitive, stereotyped behaviour and interests using quantitative, dimensional measures which are more sensitive to picking up subtle differences indicative of the BAP.

Cognitive level

Social Cognition

A wealth of research studies support the theoretical construct that people diagnosed with autism have a significantly reduced ability to process information relating to other people's mental states, commonly referred to as a Theory of Mind (e.g. Baron-Cohen et al. 1997, Baron-Cohen et al. 2001a, Happé 1994, White et al. 2009). These deficits in social cognition appear to be a key component of clinical autism, although they are not necessarily universal to people with autism, or specific to this disorder (Pellicano 2011). Early studies suggested that Theory of Mind deficits were not part of the BAP e.g. Ozonoff et al. (1993) found no differences in performance on a second-order belief

attribution task and two other Theory of Mind tasks between the siblings of children with autism and two clinical control groups. However, sample sizes were small and measures may not have been sufficiently sensitive to pick up subtle differences indicative of the BAP. Later studies have generally found that relatives of autistic probands score significantly lower on specific performance measures of social cognition ability. A very well replicated finding is that relatives of people with autism tend to perform poorly on the 'Reading the Mind in the Eyes' Test (Baron-Cohen et al. 2001a) where participants have to identify complex psychological states from looking at pictures of the eye region of people's faces (Baron-Cohen and Hammer 1997, Dorris et al. 2004, Losh and Piven 2007; but see Gokcen et al. 2009). These studies collectively suggest that older relatives of autistic probands experience mild difficulties on Theory of Mind tasks. Few studies have examined Theory of Mind ability in younger siblings of children with autism. Shaked et al. (2006) tested siblings aged 54-57 months on two measures of Theory of Mind: the false belief task and the three easiest stories from the 'Strange Stories' task (Happé 1994). No differences were found between siblings of children with autism and a typically developing control group, but the measures used may not have been sufficiently sensitive to detect subtle Theory of Mind difficulties in siblings.

Social cognitive difficulties appear not to be restricted to advanced theory of mind tasks such as the Reading the Mind in the Eyes test, but are also reported for tests of basic emotion recognition. For example, Palermo et al. (2006) asked parents of autistic probands to identify schematic facial patterns representing five 'basic' emotions, including happiness, anger, sadness, surprise and disgust. In identifying facial displays

representing sadness and disgust, fathers of autistic probands performed worse than mothers of autistic probands. Both parents performed less well on average than controls, suggesting that difficulties understanding facial expressions extend beyond the clinical boundaries of autism to include relatives of autistic probands. Likewise, Wallace et al. (2010) reported significantly reduced performance on a test of basic facial emotion recognition in parents and siblings of children with autism from multiple-incidence autism families; relatives were significantly worse at identifying expressions of fear and disgust compared to typical controls from the general population. Similarly, a study by Bölte and Poustka (2003) detected poorer performance in the recognition of facial affect in the first-degree relatives of individuals with autism from multiple-affected families compared to single-affected families. However, Bölte and Poustka found no significant differences overall between autism parents and controls. Altogether, most recent studies support earlier findings in smaller samples of autism relatives, which described difficulties recognising emotions (Smalley and Asarnow, 1990).

Other important studies on the BAP and social cognition include Losh et al. (2009), where 38 probands with autism, 83 parents of a child with autism and a control group were examined using a variety of neuropsychological tests assessing participants' social cognition, executive functioning and central coherence (see later). Parents were divided into discrete 'BAP +' and 'BAP -' groups based on the presence or absence of rigid/perfectionistic personality traits using an interview measure called the Modified Personality Assessment Schedule, Revised (Piven et al. 1994). Autistic probands and parents who were 'BAP +' were found to differ from controls on just one set of measures;

those involving social cognition. These measures included the ‘Reading the Mind in the Eyes’ task, a task assessing people’s trustworthiness of faces and a ‘Movie Stills’ task that assesses people’s reliance on facial information to discern the emotional content of complex scenes.

These studies collectively suggest that a subset of the relatives of autistic probands struggle to recognise or represent other people’s thoughts and emotions. However, despite these findings, it is still unclear whether poorer performance on Theory of Mind tasks represents a categorical entity of the BAP that is present in a subset of relatives *or* a set of continuously distributed traits that are significantly lower than population averages.

A small number of social cognition studies suggest that face processing strategy might be a component of the BAP. Adolphs et al. (2008) used a specially-devised ‘bubbles’ method (Gosselin and Schyns, 2001) to hide particular regions of the face during an emotion recognition task. Participants had to identify whether facial stimuli were ‘happy’ or ‘sad’ using information from specific features of the face. Parents of children with autism classified as socially aloof (‘BAP+’) performed at near-identical accuracy on the task compared to parents of children with autism who were not classified as socially aloof (‘BAP-’). However, the ‘BAP+’ group displayed reduced processing of information from the eye region of the face and enhanced processing of the mouth, relative to the ‘BAP-’ group.

Other studies investigating social cognition in autism relatives suggest that face memory and face recognition could be components of the BAP. Parents of children with autism were significantly impaired on the Cambridge Face Memory Test (Duchaine & Nakayama, 2006) compared to parents of typically developing children, whilst significant parent-proband correlations were found for a face matching task, suggesting that face recognition is heritable (Wilson et al. 2010). Given the large variability in performance on particular social cognition tasks by individuals on the autism spectrum, Wilson et al. stress that finding correlations within particular families can be as informative as finding significant differences between controls and experimental groups such as individuals with autism and their first-degree relatives. A study by Wallace et al. (2010) also suggests that impaired face recognition is part of the BAP; the relatives of children with autism from multiple-incidence autism families were less successful at discriminating subtle differences between digitally altered pictures of faces compared to a control group from the general population. Difficulties appeared to relate specifically to social stimuli since relatives did not show similar difficulties discriminating differences between objects (pictures of houses). Despite these positive findings, significant differences between autism relatives and control groups have not always been found on tests of facial recognition (e.g. Palermo et al. 2006 and Wilson et al. 2010).

Finally, there is evidence to suggest that relatives of autistic probands experience comparable but milder problems processing eye gaze. Wallace et al. (2010) reported differences between autism relatives and controls on a directional judgement task examining eye gaze processing. Participants had to judge the direction of social (eye

gaze) and non-social (arrow) cues which were presented on a screen for very short time durations. Relatives of children with autism did not show an accuracy advantage for detecting direct compared to averted gaze, whilst controls did. Autism relatives therefore appear less sensitive to direct eye gaze than controls from the general population. Furthermore, problems using eye gaze to orient towards targets have been reported by Scheeren and Stauder (2008). Using a similar directional judgement paradigm involving the detection of targets using social (eyes) and non-social cues (arrows), Scheeren and colleagues found that fathers of autistic probands responded slower on social cues than control fathers (see ‘visual attention, sensory integration and sensorimotor functioning’ section).

In summary, studies currently provide strong support for the inclusion of social cognitive traits in the later BAP. These include problems recognising basic facial expressions of emotion, higher order Theory of Mind difficulties (e.g. reading the mind in the eyes), mild problems processing people’s eye gaze and possibly mild difficulties discriminating/remembering faces (see Table 2 on pages 99-102). Less support has been found for social cognitive deficits in young siblings of children with autism (e.g. Shaked, 2006), although more research needs to be conducted on this experimental group examining social cognitive abilities.

Executive Function and visuospatial memory

Executive function is an umbrella term describing a collective set of functions such as planning, working memory, impulse control, inhibition, mental flexibility and the

initiation/ monitoring of actions (Hill 2004). Executive dysfunction is frequently cited as a leading theoretical construct purporting to explain autism symptomatology (e.g. Ozonoff et al. 1993). Do the relatives of autistic probands show milder manifestations of executive functioning problems? Studies assessing executive function in the relatives of people with autism have generated mixed findings. For example, Bölte and Poustka (2006) found no differences in test scores of executive function between parents of individuals with autism and parents of individuals with early onset schizophrenia or intellectual disability; experimental and control groups were matched for age and non-verbal IQ. The executive function tests used included: (1) the Wisconsin Card Sorting Test (Heaton et al. 1993), which measures a person's ability to flexibly shift cognitive strategies, form abstract concepts and respond to changes in the environment using feedback (2) the Tower of Hanoi Test (Simon, 1975), which measures higher order planning abilities and (3) the Trail Making Test (Reitan, 1979), which measures a person's speed and accuracy of attention and capacity to shift strategies in response to changes in the environment. Likewise, Losh et al. (2009) reported no significant differences on the Tower of Hanoi and Trail Making Test between BAP parents/proband and controls and Pilowsky et al. (2007) found no differences in performance on the Tower of Hanoi and Word Associations Test (Semel et al. 1995) between autism siblings and two clinical control groups (siblings of children with learning disabilities and developmental language delay). These studies contrast with early findings by Ozonoff et al. (1993) who reported significant differences in performance on the Tower of Hanoi between the siblings of children with autism and two clinical control groups. Similarly, Hughes et al. (1999) reported that a greater number of autism siblings performed poorly

(compared to a clinical and non-clinical control group) on three executive function tasks from the Cambridge Neuropsychological Test Automated Battery (Robbins et al. 1994), including the Intra-Dimensional/ Extra-Dimensional Set Shifting Task (measuring attentional flexibility) and the Tower of London (measuring planning ability; Shallice 1982). Likewise, studies by Delorme et al. (2007) and Nydén et al. (2011) found impairments in planning ability, based on poorer performance on the Tower of London by the unaffected siblings and parents of children with autism compared to a control group from the general population. However, poorer performance on the Tower of London (relative to healthy controls) was also found in the relatives of children diagnosed with Obsessive Compulsive Disorder, so impaired planning ability may not relate specifically to the relatives of autistic probands (Delorme et al. 2007). Other reports of significantly reduced planning capacities in older relatives of autistic probands compared to control groups, include Piven and Palmer 1997 (lower test scores on the Tower of Hanoi) and Hughes et al. 1997 (lower test scores on the Tower of London). However, neither study matched parent groups for non-verbal IQ; the former found significant differences between groups on non-verbal (performance) IQ whilst the latter matched parent groups by child IQ and age. In contrast, Wong et al. (2006) did not find significant reductions in planning and inhibition amongst autism relatives, when matched with a control group for chronological age, performance IQ and verbal IQ, but instead found poorer performance on a test of generativity (ideational fluency). Given that generativity problems have also been reported for autistic probands (e.g. Dichter et al. 2009), it is possible that these impairments may be genetically associated with autism. However, these studies contrast with others that provide mixed or negative support for

other kinds of generativity tasks such as verbal/ design fluency (e.g. Delorme et al. 2007, Pilowsky et al. 2007, Schmidt et al. 2008).

Other recent positive results on executive functioning tasks include a study by Sumiyoshi et al. (in press) who reported similarities in performance by individuals with autism and their siblings on the Wisconsin Card Sorting Test and a test of working memory; the Verbal Learning Task (Gold et al. 1992). Compared to a control group, both individuals with autism and their siblings recorded an elevated rate of perseverative errors on the Wisconsin Card Sorting Test and displayed a diminished ability to record the number of exemplars in the same category during the Verbal Learning Task. Experimental and control groups were matched by age but there were significant differences in IQ amongst the groups, meaning that the differences found could have been due to general cognitive ability differences rather than a selective impairment in executive functioning.

Other studies examining executive functioning processes have focused on working memory. Koczat et al. (2002) reported spatial working memory deficits during a delayed oculomotor task in the parents of autistic probands. However, some studies support superiorities on the spatial span task, which assesses visuospatial working memory (e.g. Hughes et al. 1999, Mosconi et al. 2010) These findings contrast with others in older relatives that have found no differences on working memory tasks (e.g. Hughes et al. 1997, 1999, Wong et al. 2006). In younger relatives, a study by Noland et al. (2010) found *enhanced* working memory for non-social targets in at-risk infant siblings of children using a delayed-response task. Taken together, the results of studies examining working memory in autism relatives are inconsistent.

In summary, the findings from BAP studies focusing on executive functioning have been mixed, and differences between relatives of people with autism and controls tend to diminish when groups are matched for general cognitive ability. Moreover, executive functioning difficulties are not specific to autism but can be found in a number of psychiatric conditions, such as attention deficit/ hyperactivity disorder and schizophrenia (e.g. Bölte and Poustka 2006). Therefore, whilst executive function problems may be a prospective feature of the BAP, its low specificity needs to be taken into account when deciding whether such problems indicate a specific genetic liability for autistic traits in relatives. In addition, the executive function tasks may not be efficiently tapping into specific, unitary cognitive processes and so better measures are needed to determine which cognitive operations might be disrupted in autism and the BAP (see Ozonoff et al. 1993). With this caveat in mind, the best supported prospective BAP traits in this cognitive domain include superior performance on the spatial span task and higher level planning deficits. There is also early support for ideational fluency difficulties (see Table 2). However, in general studies investigating executive functioning processes have yielded mixed results so it is not clear whether any component of this cognitive domain is a definitive feature of the BAP.

Visual attention, sensory integration and sensorimotor functioning

Some studies have found significant differences in visual perception or attention in autistic probands compared to control groups (e.g. Jolliffe and Baron-Cohen 1997, Shah and Frith 1983). This is hypothesised to reflect a different ‘cognitive style’ that leads to superior performance on tests where local visual processing is an advantage, including the Embedded Figures Task (Witkin et al. 1971; e.g. Grinter et al. 2009, Jolliffe and

Baron-Cohen 1997, Shah and Frith 1993; but see White and Saldaña, in press) and the Block Design Task (Weschler 1949; Shah and Frith 1993). There is evidence to suggest that a similar local processing style is manifested to a lesser extent in first-degree relatives, for example, Baron-Cohen and Hammer (1997) and Bölte and Poustka (2006) reported significantly faster times on the Embedded Figures Task in the parents of autistic probands compared to controls, indicating a similar tendency towards local visual processing. Superior performance on the Embedded Figures Task by fathers of autistic probands was also reported by Happé et al. (2001) together with a reduced susceptibility to visual illusions, perhaps reflecting important differences in visual processing and attention. Other studies reporting superiorities in visuospatial abilities in autism relatives include Smalley and Asarnow (1990), where siblings of autistic probands performed above average on the Block Design Test and the Benton Test of Line Orientation (Benton et al. 1975). Despite these positive findings, there have been a number of studies that have failed to find support for a local processing style in the relatives of autistic probands, especially the Block Design Test (Bölte and Poustka 2006, Fombonne et al. 1997, Losh et al. 2009, Piven and Palmer 1997, Scheeren and Stauder 2008) but also the Embedded Figures Task (e.g. Losh et al. 2009). This mirrors problems replicating a local processing style across tasks and domains in clinical cases of autism (see White and Saldaña, in press).

Whilst a number of studies on autistic probands and their relatives have found superior performance on tasks requiring strong attention to detail, studies assessing divided attention indicate possible impairments in people with autism and their relatives. In a study by Belmonte et al. (2010), participants had to simultaneously attend to spatially

disjoint, non-social stimuli and suppress intervening distractive information. Therefore, the task required a 'complex' form of processing that involved rapidly processing and integrating information from multiple inputs (in this instance, requiring selective attention to colour and orientation of stimuli in disjoint, peripheral locations). Results showed that the autism proband group performed worst on the divided attention task, followed by the siblings of the probands followed by age and IQ-matched controls. This finding suggests that divided attention problems could be a reliable candidate trait for the BAP.

As well as difficulties attending to different stimuli at the same time, relatives of autistic probands may also experience problems shifting attention. A study by Scheeren and Stauder (2008) suggests that fathers of children with autism exhibit disturbances in the engagement of attention. This conclusion was based on differences in time patterns on a reaction time task which examined shifts of attention in response to social and non-social cues. Visual attention patterns have also been examined in younger infant siblings of children with autism as an early indicator of the BAP (see also 'reciprocal social interaction' section). The results of current studies are slightly mixed but there is some evidence that siblings who are at-risk for autism display early problems disengaging from stimuli and spend longer periods attending to non-social stimuli (e.g. see Ibanez et al. 2008 and Bhat et al. 2010). Similar findings were reported by Elsabbagh et al. (2009b) who tested 9-10 month old siblings of autistic probands using a visual orienting task that measured the time taken to disengage from a central stimulus in order to fixate on a peripheral one. Infant siblings of autistic probands exhibited longer disengagement latencies compared to a control group, indicating problems with the early-developing

ability to switch attention flexibly. Autism siblings were also worse at automatically orienting to visual targets and forming expectations about their visual environment. A study by Holmboe et al. (2010) did not find significant group differences in attentional disengagement between infant siblings and typically developing controls on a task of inhibitory control (the Freeze-Frame task; Holmboe et al. 2008). However, significantly more infants in the autism-sibling group had problems disengaging from a central stimulus compared to the control group. Therefore, problems in visual orientation, particularly attentional engagement and disengagement, are strong contenders for inclusion in the BAP. Additionally, the finding that autism siblings spend significantly longer looking at their caregiver's mouth and less time at the eyes compared to typically developing controls (Merin et al. 2007; see 'reciprocal social interaction' section) is suggestive of problems in visually attending to the most informative features of social stimuli.

Finally, a study by Mosconi et al. (2010) has detected oculomotor abnormalities in the first-degree relatives of individuals with autism. Using tests of sensorimotor responses to visual stimuli, relatives displayed saccadic dysmetria and increased variability of saccade accuracy. They also displayed left-lateralised deficits in smooth-pursuit eye movement (open-loop pursuit gain) and procedural learning for rightward saccades. Some of these results have also been found in samples of individuals with autism (e.g. Takarae et al. 2004) suggesting that alterations in the neural circuitry recruited for these tasks is a heritable component of autism and a candidate feature of the BAP. Other studies examining oculomotor functioning in first degree relatives of autistic probands include Koczat et al. (2002). Parents of children with autism were found to show significantly

poorer spatial accuracy on a delayed oculomotor response task designed to detect spatial working memory deficits compared to a sample of adult controls.

Studies therefore broadly provide support for visual attention difficulties in the first degree relatives of autistic probands, especially attentional engagement/ disengagement, divided attention and oculomotor abnormalities, with mixed findings for local visual attention biases. However, further research is needed replicating studies that report significant differences between autism relatives and controls in this cognitive domain. Future research could also examine other sensory modalities and investigate associations between the BAP and elevated sensory hypersensitivity. Some studies suggest that autistic probands detect sensory stimuli at lower thresholds (Baron-Cohen et al. 2009). It remains to be explored whether this phenomenon can also be observed (perhaps to a lesser extent) in unaffected relatives of individuals with autism.

Language Ability

To complement the investigation of language impairments in the relatives of individuals with autism using questionnaires and interviews (see ‘Language and Communication’), researchers have administered a number of performance measures of language ability. A study by Schmidt et al. (2008) investigated phonological processing in autism parents using the non-word repetition task (Gathercole and Baddeley, 1990). Schmidt reported poorer performance on this task compared to adult controls suggesting that phonological processing deficits could be a component of the BAP. Also, a study by Lindgren et al. (2009) investigated expressive language, lexical comprehension and phonological processing in people with autism, specific language impairment and their first-degree

relatives. Relatives of autistic probands were superior on tests of non-word repetition/ phonological processing compared to relatives of probands with specific language impairment. Whilst relatives of children with autism *and* language delay scored lower on measures of reading ability and receptive language than relatives of children with autism *without* language delay, no statistically significant differences were found on measures of expressive language or phonological processing. Lindgren et al. concluded that phonological deficits were not part of the heritable phenotype of autism, and so should not be included in the BAP.

A study by Losh et al. (2010) investigated Rapid Automatised Naming (RAN) ability in individuals with High Functioning Autism and their parents. Both groups exhibited significantly slower times on two rapid naming tasks (colour and object naming) compared to typically developing children and their parents. This supported a previous study that found significant differences between parents of children with autism and controls on the same two subtests of the RAN task (Denckla and Rudel, 1974; Piven and Palmer 1997). Furthermore, Losh et al. (2010) found significant associations between parents' times on these tasks and the social and language-behavioural features of the BAP, measured by the Autism Family History Interview and the Modified Personality Assessment Schedule. These features include a socially aloof/ untactful personality and retrospective reports of language delay. There was also a significant association between the RAN performance of fathers and their child with autism, suggesting that this trait is heritable. However, not all studies have found significant differences between autism relatives and controls on this measure (e.g. Pilowsky et al. 2003). It should be noted that whilst RAN tasks are an effective measure of expressive language ability, they also

involve a number of neuropsychological domains including executive control and attentional processes. Therefore, whilst RAN is a candidate trait of the BAP and a potential indicator of liability to autism, the measure does not have strong structural and functional specificity.

Performance measures that have examined receptive and expressive language ability have generally not found impairments in parents and non-infant siblings (e.g. Lindgren et al. 2009, Pilowsky et al. 2003, Schmidt et al. 2008). Studies focusing on the younger infant siblings of children with autism have provided stronger support for milder expressive/receptive language difficulties e.g. Gamliel et al. (2009) examined children between 14 and 54 months using a battery of language and general cognitive measures, reporting significant differences in language scores between typically developing controls and children later displaying the BAP at 7 years of age. Likewise, Toth et al. (2007) reported that 18-27 month old siblings of children with autism had lower receptive language skills than typically developing controls as well as displaying below average expressive language ability, using the Mullen Scales of Early Learning (Mullen 1997). However, using the Clinical Evaluation of Language Fundamentals, Levy and Bar-Yuda (2011) found no differences in language ability between infant autism siblings and typically developing controls when IQ was controlled for. Using the same measure, Stone et al. (2007) found no differences in expressive language ability between 12-23 month year old autism siblings and typically developing controls.

Finally, studies provide moderate support for poorer performance on tests of reading or spelling in the relatives of autistic probands, compared to controls (e.g. Fombonne et al. 1997 and Piven and Palmer 1997). These studies contrast with others that have reported

no differences (e.g. Freeman et al. 1989, Pilowsky et al. 2007, Whitehouse et al. 2007) or superior performance compared to other clinical groups (e.g. dyslexia; Happé et al. 2001).

Overall, studies provide moderate support for impairments in language ability, both in the early emerging BAP in infant siblings and the later BAP in older relatives. Prospective traits for the BAP include expressive or receptive language difficulties in infant siblings and impaired performance on the RAN task and poorer reading ability in older relatives. However in general the results of studies analysing language performance do not strongly substantiate the inclusion of these traits in the BAP.

Contrast Sensitivity/ Motion Perception

A very small number of research studies have examined contrast sensitivity and visual perception of motion in the relatives of autistic probands. Impaired visual motion perception has been reported in people diagnosed with autism. At a neurological level, this has been linked to the atypical functioning of the subcortical magnocellular pathway that processes visual information. This can be tested by measuring participants' contrast sensitivity for luminance and chromatic light using sinusoidal gratings that are presented at different spatial and temporal frequencies. Contrast sensitivity can be measured both for the detection of a moving stimulus and for correctly discriminating the direction that the stimulus is moving. A study by Koh et al. (2010) detected inefficient motion processing for luminance stimuli in both people with autism and unaffected siblings of individuals with autism compared to typically developing adolescents. Furthermore, the study reported significantly higher chromatic contrast sensitivity in the adolescent

siblings of autistic probands compared to typical controls. Chromatic contrast sensitivity in siblings was also higher than in autistic probands, leading Koh et al. to suggest that higher chromatic sensitivity could be a protective factor against full-scale autism. A study by McCleery et al. (2007) also reported abnormal contrast sensitivity in the younger infant siblings of children with autism, aged 6 months. Using the forced-choice preferential looking technique (Teller 1979), at-risk siblings appeared to be twice as sensitive to luminance (light/ dark) stimuli than typically developing controls whilst exhibiting identical sensitivity to chromatic (red/green) stimuli. McCleery and colleagues inferred that these results indicated atypical functioning of the magnocellular visual pathway in the at-risk sibling group as well as their autistic relatives. These studies contrast with de Jonge et al. (2007) who found no evidence for significant differences in contrast sensitivity, motion and form perception in both people with autism and parents of people with autism compared to a control group. Therefore, more research is required replicating studies examining contrast sensitivity and motion perception in autism relatives. The above positive findings in this cognitive domain must also be placed in the wider context of studies examining motion perception in people diagnosed with autism, which have yielded mixed results (e.g. de Jonge et al. 2007, Jones et al. 2011, Pellicano et al. 2005, Spencer et al. 2000).

General cognitive abilities

Intellectual disability (ID)* is common in autism, with a prevalence of approximately 70% in cases diagnosed with autistic disorder (Fombonne 2006). However, when the

* Intellectual Disability (previously referred to as mental retardation, DSM-IV) is most commonly defined by an IQ score equal to or below 70

other conditions on the autism spectrum are also included (Asperger Syndrome and PDD-nos), the prevalence of ID in autism is considerably lower (e.g. Chakrabarti and Fombonne 2005). The exact aetiological link between autism and ID is unclear, with twin studies producing conflicting results (e.g. Hoekstra et al. 2009; 2010; Taniai et al. 2008).

Studies focusing on the relatives of people with autism have generally found that intellectual disability is *not* a feature of the BAP. For example Fombonne et al. (1997) assessed the first-degree relatives of 99 autism probands and 36 Down Syndrome controls on standardised tests of intellectual functioning and did not find an increased incidence of ID among autism relatives. These results corroborated earlier findings by Freeman et al. (1989) and Szatmari et al. (1993) that found no mild cognitive deficits in the relatives of people with autism. A study by Starr et al. (2001) suggested that the liability of relatives of autistic probands to express the cognitive and social deficits associated with the BAP did not depend upon the IQ of the clinically diagnosed family member. This suggests that the BAP and general cognitive ability are largely independent of each other. Likewise, a study by Yirmiya et al. (2007) on infant siblings of children with autism did not find delays in general mental development compared to siblings of typically developing children. Altogether, these studies point towards a limited genetic association between ID and autism (Hoekstra et al. 2009) and suggest that general cognitive ability does not play a major role in the BAP.

Other Psychiatric Conditions

Studies into the BAP often show that whilst autistic probands and their relatives exhibit a number of atypicalities in different domains of functioning, similar impairments may be

found in other psychiatric conditions such as: (1) executive dysfunction in schizophrenia and attention deficit/ hyperactivity disorder (e.g. Bölte and Poustka 2006; see also Happé and Ronald 2008), (2) Theory of Mind deficits in schizophrenia (e.g. Frith and Corcoran 1996) and (3) communication difficulties in specific language impairment (e.g. Whitehouse et al. 2007). This suggests that there could be genetic or epigenetic overlap between different psychiatric conditions e.g. autism and attention deficit/ hyperactivity disorder (Rommelse et al., in press). Support for this view is provided by studies documenting the aggregation of other psychiatric disorders in autism families (see Lainhart 1999 for a review of early findings).

A number of studies have documented higher rates of affective disorder, depression, social phobia and anxiety in the relatives of autistic probands compared to control groups. Using family history and direct interviews, Piven and Palmer (1999) reported familial aggregation of other psychiatric conditions including social phobia and major depressive disorder compared to a clinical control group. Earlier studies carried out by Piven and colleagues had reported high rates of affective disorder and anxiety disorder in siblings and parents of children with autism (Piven et al. 1990, 1991). Using the Autism Family History Interview, Bolton et al. (1998) found significantly higher rates of other psychiatric conditions in relatives of autistic probands compared to a clinical control group, including major depressive disorder. Although psychiatric conditions such as affective disorders rarely occurred together with the BAP, the high familial aggregation of these conditions suggests relatives of autistic probands have an increased susceptibility to a number of different psychiatric problems. Higher rates of depression in the first degree relatives of people with autism have been reported in a range of studies, both

when comparing the rates to general population (e.g. Gold 1993, Micali et al. 2004) and clinical control samples (e.g. Smalley et al. 1995) Finally, a recent study by Ingersoll et al. (2011) reported increased depressed mood in mothers of children with autism compared to mothers of typically developing children. Furthermore, depressed mood was predicted by a measure of the BAP (combined social-communication subscale of the Autism-Spectrum Quotient) after controlling for parenting stress and the severity of the child's autism.

High rates of obsessive compulsive disorder have also been found in the relatives of autistic probands compared to control groups (Wilcox et al., 2003). Moreover, high numbers of obsessive-compulsive traits in parents have been linked to high scores in the autistic proband on the repetitive behaviour domain of the Autism Diagnostic Interview-Revised; correlations were strongest between fathers and child (Hollander et al. 2003). A study by Micali et al. (2004) on families with a child with a PDD found significantly higher rates of second-degree relatives with an obsessive compulsive disorder, whilst Bolton et al. (1998) reported higher rates of obsessive compulsive disorder in the first-degree relatives of autistic probands.

Altogether, these studies suggest that autism relatives may be at an increased risk for developing other psychiatric conditions in comparison to both non-clinical and clinical control groups; particularly obsessive compulsive disorder, anxiety, social phobia and mood disorders such as depression. Many reports of clinical depression in the parents of children with autism have an onset before the birth of the child with autism (e.g. 75% of mothers reported by Micali et al. 2004). This suggests that increased rates of psychiatric conditions (such as anxiety and major depression) may have a genetic link with autism

and are not just caused by the stress associated with looking after children with clinical diagnoses; a meta-analysis of psychiatric disorders in parents of children with autism by Yirmiya and Shaked (2005) seems to support this conclusion. Yirmiya and Shaked reported higher rates of other psychiatric conditions in the parents of children with autism compared to parents of typically developing children or children with conditions that do not have a genetic liability (e.g. Down Syndrome). However, higher rates of psychiatric conditions were also found in groups carrying other known genetic liabilities, such as language/ learning disabilities, suggesting that the familiarity of other psychiatric conditions is not an exclusive feature of autism.

Personality Traits

The personality traits of relatives of autistic probands have been extensively studied by researchers and are frequently cited as components of the BAP. These are restricted to specific personality traits, which are believed to reflect an underlying genetic liability for autism. The personality characteristics described more commonly in the relatives of autistic probands compared to relatives of typically developing children or children with another medical condition (e.g. Down Syndrome; Piven et al. 1997b) include ‘rigid’ (Hurley et al. 2007, Losh et al. 2008, Piven et al. 1997b; but see Murphy et al. 2000), ‘impulsive’ (Murphy et al. 2000) ‘aloof’ (Hurley et al. 2007, Losh et al. 2008, Piven et al., 1994; 1997b, Murphy et al. 2000), ‘shy’ (Murphy et al. 2000), ‘tactless’ (Piven et al. 1994, Losh et al. 2008; but see Murphy et al. 2000) ‘reserved/ schizoid’ (Bölte et al. 2007), ‘irritable’ (Murphy et al. 2000) ‘hypersensitive to criticism’ (Piven et al. 1997b) ‘neurotic’ (Losh et al. 2008), ‘undemonstrative’ (Piven et al. 1994; but see Murphy et al.

2000) and 'anxious' (Losh et al. 2008, Murphy et al. 2000, Piven et al. 1997b). A factor analysis carried out by Murphy et al. (2000) detected three clusters of personality traits that were more common in the relatives of autistic probands compared to relatives of Down syndrome probands; these were called 'withdrawn', 'difficult' and 'tense'. However, only the 'withdrawn' factor was significantly associated with the broader behavioural phenotype of autism, which was measured using the Autism Family History Interview. These personality traits may also be related to performance on cognitive BAP measures (see Losh et al. 2009) as well as the core behavioural domains of autism. A recent study by Seidman et al. (in press) reported sex differences in personality traits in fathers and mothers of children with autism. Using the Broad Autism Phenotype Questionnaire, fathers were rated by their respective partners as more 'aloof' than mothers, whilst mothers were rated by their respective partners as more 'rigid' than fathers. Seidman et al. note that the high ratings of 'rigidity' in mothers could be due to pressure to adapt to a rigid lifestyle in order to make their autistic child's environment more predictable and structured. Further research could investigate the relationship between the personality traits of autism relatives and the increased risk to developing other psychiatric conditions (e.g. anxiety and depression), and the association between these traits and neuroanatomy and neurofunctionality. These latter topics will be the focus of the next paragraph.

Neuroanatomical and neurofunctional correlates of the BAP

A complementary level of analysis for understanding the aetiology of autism is to examine potential neuroanatomical and neurofunctional correlates of autistic traits and to determine whether these correlates extend to the relatives of autistic probands. Autism has been linked to an acceleration of brain growth at around 12 months of age, with macrocephaly found in 15-20% of diagnosed children by 4-5 years of age (Minschew and Williams 2007). Neuroimaging data provides evidence for abnormal growth in grey and white matter which are responsible for processing and transferring information between brain regions (Amaral et al. 2008, Courchesne et al. 2007, Schumann et al. 2010). In particular, there is atypical growth in the frontal and temporal lobes and in structures within the limbic system such as the amygdala. These regions are heavily involved in social behaviour and communication (Amaral et al. 2008, Courchesne et al. 2007). Neuroimaging studies also show differences in patterns of activation, with information taking a longer time to be processed throughout the brain of individuals with autism (Belmonte et al. 2010, Gepner and Féron 2009). This is hypothesised to be a consequence of local over-connectivity and long-range underconnectivity between separate functional brain regions (Belmonte et al. 2004). A small number of studies have reported functional local over-connectivity in the brains of individuals with autism during behavioural tasks (e.g. Schmitz et al. 2006). In contrast a large number of studies have detected long-range functional under-connectivity, such as Kleinhans et al. (2008) who found disconnections between the fusiform face area, left amygdala, posterior cingulate and thalamus during a face processing task (see Wass 2011 for a review of connectivity studies). In general, brain imaging studies suggests there is less functional connectivity between brain regions linked to perception, social cognition, language and problem-solving in individuals with

autism (Belmonte et al. 2004, Courchesne et al. 2007, Minshew and Williams 2007, Isler et al. 2010).

Have similar findings been reported in the relatives of autistic probands? A number of studies have examined functional differences in regions comprising the ‘social brain’, including the amygdala, superior temporal sulcus, fusiform face area, orbitofrontal cortex and anterior cingulate cortex (Brothers 1990, Spencer et al. 2011). These are documented below, followed by studies examining other brain regions and behavioural paradigms as well as studies examining neurostructural differences in autism relatives.

Mentalising/ emotion recognition

A preliminary fMRI study on 12 parents of children with Asperger Syndrome by Baron-Cohen et al. (2006) indicated atypical brain activity during the Reading the mind in the eyes task, relative to sex- and IQ-, but not age-, matched controls from the general population. There was reduced activity in the mid temporal gyrus and the inferior frontal gyrus during completion of the mentalising task in the parents of autistic probands compared to gender-matched controls. Similarly, Spencer et al. (2011) reported significantly reduced fMRI activity in a group of siblings of autistic probands when responding to happy versus neutral faces during an emotion recognition task. Relative to an adolescent control group, attenuated activity was found in a variety of regions associated with socio-emotional functioning, including the Fusiform Face Area and the Superior Temporal Sulcus. Therefore fMRI response to happy faces could be a sensitive neuroimaging marker of the BAP.

Face Processing

Neurofunctional correlates of the BAP were also assessed using fMRI by Dalton et al. (2007) who detected significantly reduced levels of gaze fixation in the unaffected siblings of autistic probands compared to typically developing controls in response to a face-processing task. This was reflected in decreased activity within the right hemisphere of the fusiform gyrus which is involved in processing faces and gaze direction. The results for siblings were intermediate between those for typically developing controls and the autism group, who showed significantly reduced *bilateral* activity in the fusiform gyrus. However, Dalton et al.'s use of eye tracking data suggested that, rather than there being abnormalities in the fusiform region of the brain, there are problems with how faces are scanned and which facial cues are attended to, these having a 'downstream' effect on fusiform activity. In addition, unlike some autism samples, the siblings of autistic probands did not display heightened activation in the affective neural circuitry in response to human faces..

Biological motion processing

Kaiser et al. (2010) found commonalities in brain activity between children with autism and their siblings in response to a task assessing sensitivity to biological motion using point-light displays. Results implicated shared areas of atypical function in the left dorsolateral prefrontal cortex, the right inferior temporal gyrus and the bilateral fusiform gyrus. Importantly, siblings who exhibited subtle social and communication difficulties were excluded. The authors suggest that at a neurological level, genetic relatives of

individuals with autism share subtle disruptions in brain function that are not necessarily picked up at a behavioural level. The authors further speculate that brain response to biological motion reflects a genetic vulnerability to autism in relatives of individuals with autism that may be compensated for during development by unique areas of activation in the ventromedial prefrontal cortex and right posterior superior temporal sulcus.

Visual Attention

Brain activity during a visual search task was investigated for 12 parents of children with Asperger Syndrome by Baron-Cohen et al. (2006). The results of fMRI scans indicated reduced activation of the right middle occipital gyrus and the left lingual gyrus during completion of the visual search task, relative to sex and IQ-matched controls. Likewise, fMRI was used by Belmonte et al. (2010) in a study assessing visual attention in autistic probands and clinically unaffected brothers. Both probands and brothers performed significantly less well on a visual divided-attention task (see ‘visual attention, sensory integration and sensorimotor functioning’ section) which at a neurobiological level was detected by atypical fronto-cerebellar activation correlating with the psychometric measures of autistic traits. Results on the divided-attention task suggested that both autism probands and, to a lesser degree, their siblings displayed atypical spatial distribution of visual attention. Neuroimaging data showed that in the autism group, posterior cortices linked to lower-level processing were over-active and frontal cortices were under-active; in the autism-sib group, differential activation between conditions was much more limited. The fronto-cerebellar attention systems were activated in the autism and sib-autism group but were time-delayed, suggesting that it was the differential timing

of activation that was causing poorer performance, rather than differences in activation *per se*. Despite showing a similar response to the autism group, stronger activity was measured in the prefrontal brain regions of the unaffected sibling group. The authors suggest that the stronger activity may be a compensatory strategy for differences in neural processing that ensured connectivity was maintained between different brain regions recruited for the task.

Executive Function

Kawakubo et al. (2009) examined prefrontal cortex activation in the unaffected siblings of autistic probands during an executive functioning task (the letter fluency task).

Kawakubo and colleagues examined brain activity by measuring changes in haemoglobin concentration in the prefrontal cortex using near-infrared spectroscopy. Siblings ranged in age from 5 to 39 years; in child siblings, there were no significant changes in haemoglobin concentration relative to controls but for adult siblings, increases in haemoglobin was intermediate between controls and adults with autism, despite similar behavioural performance on the task across the three groups. Unaffected siblings showing evidence of the behavioural BAP with a questionnaire called the Childhood Autism Rating Scale-Tokyo Version (Kurita et al. 1989) were removed from analyses suggesting that neurofunctional measures were sensitive at detecting differences between first degree relatives and controls that are not picked up at a behavioural level.

ERP Studies and the BAP

In addition to using MRI to assess the neuroanatomy and neurofunctional correlates of the BAP, electrophysiological studies have provided further evidence for neurofunctional differences in relatives of autistic probands compared to controls. An event related potential (ERP) study (Dawson et al. 2005) on the parents of autistic probands found an absence of right-hemisphere lateralised augmentation of the N170 ERP to faces as well as a shorter latency N170 to faces (versus objects). This result mirrors the pattern seen in individuals diagnosed with autism (e.g. Dawson et al. 2002). Other studies using ERP include Elsabbagh et al. (2009a) which found that both autistic probands and their infant siblings displayed a prolonged latency in the ‘P-400’ component in response to direct eye gaze compared to controls,. This result suggests that the response to eye gaze in relatives of autistic probands was delayed and less persistent.

MEG Studies and the BAP

Other studies have examined neurofunctional correlates of the BAP using magnetoencephalography (MEG). Rojas et al. (2011) took MEG recordings of 21 parents of autistic probands and 21 adult controls reporting a reduction in steady-state gamma-band responses in the autism-parent group, similar to the responses of children diagnosed with autism (e.g. Wilson et al. 2007). Measures showing a reduction in autism-parents included ‘Gamma-band phase locking factor’ and ‘phase-locked power’. Furthermore, correlations were found between Gamma-band phase locking factor and the ‘communication’ subscale of the Autism-Spectrum Quotient. Rojas et al. reported that the behavioural measures of the BAP (Social Responsiveness Scale and Autism-Spectrum Quotient) did not strongly distinguish groups whilst biological markers derived from the

MEG recordings seemed to be more sensitive at picking up differences between autistic probands, first degree relatives of autistic probands and controls.

Structural MRI and the social brain in autism relatives

A very small number of studies have investigated structural differences in the social brain of autism relatives. A study by Dalton et al. (2007) found a significant reduction in the volume of the amygdala in siblings of people with autism compared to controls.

However, no group difference in amygdala volume was detected between autism parents and controls in a study by Peterson et al. (2006). There is therefore currently limited evidence for structural differences in brain regions connected to the social brain in the relatives of autistic probands

Other structural neuroimaging studies in autism relatives

Other structural MRI studies include Rojas et al. (2004) who reported that the parents of children with autism had significantly larger left hippocampus volumes compared to controls from the general population. However, these results failed to replicate in a study by Peterson et al. (2006). Peterson and colleagues carried out a structural MRI study of gray matter in the parents of autistic probands. The scans revealed differences, relative to adult controls, in regions functionally associated with social-cognitive and motor processes that are impaired in autism. Using voxel-based morphometry, Peterson et al. reported an increase in gray matter in the inferior and medial frontal gyri and cerebellum. Both Rojas et al. (2004) and Peterson et al. (2006) reported no significant differences in total brain volume between experimental and control groups. These studies, however,

contrast with Palmen et al. (2005) who found no significant differences in the volume of *any* brain regions between autism parents and controls using structural MRI. Finally a structural MRI study by Branchini et al. (2009) reported no significant difference in total/ regional corpus callosum area between the siblings of children with autism and age/IQ-matched controls.

Structural investigations of the BAP also include Diffusion Tensor Imaging. A study by Barnea-Goraly et al. (2010) used Diffusion Tensor Imaging to investigate differences in white matter in children with autism, their unaffected siblings and controls. Barnea-Goraly and colleagues carried out a whole brain analysis using tract-based spatial statistics and found significantly reduced white matter fractional anisotropy values in both the autism and autism-sibling group, relative to age and IQ-matched controls. Areas where aberrant white matter was detected included the medial prefrontal and superior temporal regions and the temporo-parietal junctions. Reductions were found in axial diffusivity but not radial diffusivity suggesting that the alterations were in fiber coherence rather than myelination. However, no significant correlations were found between white matter functional anisotropy/ axial diffusivity and autism symptomatology. Furthermore, unaffected siblings were excluded if they displayed behavioural features of the BAP using the Autism Family History Interview. Therefore, DTI measures may be more sensitive to subtle differences in the first degree relatives of autistic probands and controls indicative of the BAP at a biological/ neurostructural level.

Summary

Neurofunctional and neuroanatomical studies of autistic probands and their relatives using neuroimaging techniques such as fMRI, sMRI, EEG, MEG and DTI have started to reveal important differences in brain structure, activity and connectivity in and between regions of the brain. Such studies have proven essential in furthering our understanding of the neural correlates of the cognitive aspects of autism (e.g. sensory perception, social cognition and visual attention, see Table 3 on pages 103 and 104). Future studies should continue to search for neural underpinnings of BAP expression at a cognitive and behavioural level. These studies are still in their infancy and more neuroimaging research is required to determine the extent to which autistic probands and their first degree relatives share atypicalities in brain structure and function. Furthermore, these studies warrant replication in order to protect against possible publication biases in the neuroimaging research literature (see Ioannidis, 2011).

Summary of findings and future directions

In this review we have summarised the research studies that have taken place over the last 20-30 years on the BAP from multiple, mutually reinforcing categories of analysis. The list of prospective traits for the BAP discussed here is not exhaustive and in the future must include a more thorough and diverse examination of domains of functioning associated with autism such as sensory hypersensitivity and motion processing/ detection (e.g. see Bertone et al. 2003, Bonnel et al. 2003, Gepner and Féron 2009, Gepner and Mestre 2002 and Leekam et al. 2007). Nevertheless, a wide variety of traits has been examined for inclusion in the BAP; this firstly includes the possibility of an early

emerging BAP in the younger infant siblings of children with autism. Candidate traits include language delay and social deficits such as atypicalities in gaze shift patterns, reduced requesting behaviour, initiation of joint attention and responding to joint attention (see Table 1). Studies also report early problems in visually disengaging from stimuli, whilst more research is needed investigating executive function and Theory of Mind in at-risk infant siblings. However, many of the research studies conducted on at-risk siblings in this review have not reassessed this experimental group when the siblings are older than three years of age so it is not clear whether autistic traits displayed in at-risk siblings are part of the full autism phenotype or isolated traits indicative of the BAP. This methodological constraint does not apply for older siblings and parents of autistic probands.

In older siblings and parents, positive findings at a behavioural level have been most consistently reported for pragmatic language skills, social responsiveness and other areas of reciprocal social interaction. More research needs to examine restricted, repetitive interests in the relatives of people with autism. Of particular interest is the question of whether the BAP is restricted to specific aspects of this behavioural domain, such as circumscribed interests or a rigid/ perfectionistic style, or whether it applies more broadly, including repetitive motor activities and resistance to change.

At a cognitive level, the BAP has most consistently been found for social cognition e.g. complex mental state recognition, emotion recognition and face processing strategy. It is less clear whether executive functioning is part of the BAP. Findings in this area have

been less consistent and a number of studies finding impairments did not appropriately match experimental and control groups for IQ (e.g. Hughes et al. 1997, Piven and Palmer 1997). In contrast, a number of studies investigating social cognition in autism relatives matched control groups for IQ (e.g. Baron-Cohen and Hammer 1997, Dorris et al. 2004, Gokcen et al. 2009), although there are exceptions (Losh and Piven 2007). Results are also mixed for studies assessing local visual processing in the relatives of individuals with autism. Other areas of cognition requiring further research include divided attention and engagement/ disengagement of attention to social and non-social stimuli. It should be noted that the conflicting results reported in this review must be set in the wider context of autism research, where deficits in cognitive domains such as executive function or Theory of Mind are neither specific nor universal in people clinically diagnosed with autism. Lastly, interview and questionnaire-based measures indicate an elevated rate of personality traits in the BAP, including ‘aloof’, ‘rigid’ and ‘hypersensitive’ as well as elevated rates of other psychiatric conditions in autism families, such as anxiety and depression.

Future studies should use quantitative, continuous behavioural measures that have sufficient sensitivity to record subclinical autistic traits. Secondly, it is important to ensure that the participants used to examine the BAP do not qualify for a formal diagnosis of autism (Hoekstra and Wheelwright 2010). Furthermore, experimental and control groups should be matched for general cognitive functioning to ensure that differences on particular cognitive tasks represent a specific and selective impairment in functioning and cannot be attributed to general cognitive impairment. The selection of

experimental groups must also be scrutinised; splitting up the genetic relatives of autistic probands into ‘BAP+’ and ‘BAP-’ groups may lead to different results compared to studies that analyse average differences between autism relatives and controls.

Researchers should bear the possible impact of these methodological differences in mind and should be explicit about their methods in future papers, so that we can improve our understanding of conflicting findings.

Future research could also help to better understand the genetic aetiology of the BAP. A number of studies suggest that subthreshold autistic traits aggregate in multiple-incidence (‘multiplex’) autism families and occur less frequently in single-incidence (‘simplex’) autism families (e.g. Constantino et al. 2006; 2010, Virkud et al. 2009). It is thought that these findings reflect differential modes of genetic transmission of autistic traits in simplex and multiplex families; the aetiology of simplex autism may be more strongly influenced by rare, *de novo* genetic mutations or copy number variations of large effect, whilst the aetiology of multiplex autism is more strongly influenced by inherited gene variants (Levy et al. 2011, Marshall et al. 2008, Sanders et al. 2011, Sebat et al. 2007). More studies are needed examining the expression of the BAP in simplex and multiplex families in order to further test the hypothesis of differential modes of genetic transmission in autism families. Of particular relevance would be studies examining whether the stronger expression of the BAP in multiplex compared to simplex families applies to the BAP as a whole, or only to particular aspects of the BAP.

Another important objective for future studies is to search for associations across different levels of analysis, such as between: (1) observational reports of behaviour, (2) performance measures and instruments that systematically examine cognition, (3) systematic accounts of personality and other psychiatric conditions, and (4) brain scanning techniques that record the underlying neural substrates involved. It is through these studies that we can improve our understanding of the developmental pathways leading to autism. Neuroimaging studies, described in this review, should in particular start to shed light on these developmental pathways. These include connectivity/functional MRI studies examining regions of the social brain (e.g. Dalton et al. 2007, Spencer et al. 2011), as well as other structures (e.g. the cerebellum; Belmonte et al. 2010). DTI, ERP and MEG studies of autistic probands and their relatives are also starting to provide further useful ways of exploring the neurodevelopmental pathways leading to autism by better understanding its biological liability (e.g. Elsabbagh et al. 2009a, Rojas et al. 2011).

Studies on the BAP can help to identify which characteristics aggregate in family members and are thus likely to be promising endophenotypes for autism. Through the use of endophenotypes (see Gottesman and Gould 2003) we can restrict the phenotypic heterogeneity and increase the power to detect vulnerability genes for autism. Such an approach has been advocated by researchers in the field of autism genetics (e.g. Leboyer et al. 1998, Le Couteur et al. 1996, Smith et al. 2009, Weiss 2009) as well as in behavioural genetics more broadly (e.g. deGeus 2002, de Geus and Boomsma 2001; Gottesman and Gould 2003). The evidence as collated in Table 1 and 2 provides pointers

to the most promising behavioural and cognitive endophenotypes for autism (including pragmatic difficulties, language delay, reduced social responsiveness, poorer social skills, theory of mind difficulties, emotion recognition difficulties and poorer performance on visual divided attention/ social orienting tasks). Table 3 gives preliminary suggestions for endophenotypes at the neural level.

Molecular genetic studies of autism have currently been most successful in detecting rare gene variants and rare copy number variations with large effects (Abrahams and Geschwind 2008; Freitag et al. 2010; Pinto et al. 2010). Studies examining the role of common gene variants affecting the risk for autism have been less consistent and are hampered by lack of replication (e.g. Anney et al. 2010). Common autism gene variants are likely to be of weak effect, and typically require very large sample sizes in order to have sufficient power to be detected. If studies on the BAP detect similar but milder manifestations of autistic traits in the relatives of autistic probands, this opens up the possibility to include relatives with subthreshold autistic traits in genetic linkage and association studies that explore common inherited variants linked to autism. It is therefore extremely important to obtain reliable, quantitative measures of autistic traits that are likely to be under genetic influence, so that these measures can be applied in future genetic studies of autism. Some previous studies using quantitative measures of autistic traits have reported significant association or linkage findings using both general population (e.g. Pourcain et al. 2010) or clinical samples (e.g. Duvall et al. 2007), illustrating the usefulness of this approach. Studies of the BAP are instrumental in

determining which aspects of the BAP show the most promise for inclusion in genetic studies.

Finally, research studies on the BAP may assist in providing additional support and guidance to other members of the family that contain people on the autism spectrum; for example, fathers of children with autism who display the BAP could be offered advice about how to manage and improve their relationships with peers and other members of the family. Research into the BAP could help guide the implementation of this type of support.

Studies on the BAP will continue to offer valuable insights by bringing researchers closer to the genetic aetiology and neurobiological pathways underlying autism. This will be achieved by fully analysing and exploring the behavioural and cognitive features of the BAP and linking these to underlying brain anatomy and function. We hope this review will assist in contributing to that aim.

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Table 1. *An early emerging BAP? A summary of research studies reporting autistic traits in the ‘at-risk’ infant siblings of autistic probands.*

	Category	Candidate Traits	Support in research literature* (number of studies reviewed)	Measures used (examples)
Behavioural level	1. Language and communication	<ul style="list-style-type: none"> • Semantic-pragmatic language • Language delay • Rate of communicating 	++ (1) sig. levels not reported (3) ++ (1)	<ul style="list-style-type: none"> • Autism Diagnostic Observational Schedule (Ben-Yizhak et al. 2011) • Communication and Symbolic Behavior Scale Developmental Profile (Toth et al. 2007)
	2. Motor development	<ul style="list-style-type: none"> • Reduced time spent in different postures 	++ (1)	<ul style="list-style-type: none"> • Videotape rating of posture bouts (Iverson and Wozniak 2007)
	3. Social interaction	<ul style="list-style-type: none"> • Response to name • Initiation of Joint Attention • Response to Joint Attention • Joint attention (combined) • Reduced requesting behaviours • Response to Social Interaction • Atypical gaze shifting • Reduced social smiling/ higher rates of ‘neutral affect’ during FFSF task • Weaker mother-infant synchrony for infant-led interactions during free play • Reduced gaze towards caregiver’s eyes, relative to 	- / + (2) + (3) + (5) - - (1) + (4) ++ (1) - / + (5) + (3) ++ (1) ++ (1)	<ul style="list-style-type: none"> • Responding to Name task (Nadig et al. 2007) • Early Social Communication Scales (Goldberg et al. 2005) • Responding to Joint Attention task (Presmanes et al. 2007) • Communication and Symbolic Behavior Scale Developmental Profile (Toth et al. 2007) • Early Social Communication Scales (Goldberg et al. 2005) • Early Social Communication Scales (Goldberg et al. 2005) • The face-to-face/ still-face paradigm (Cassel et al. 2007, Merin et al. 2007) • The face-to-face/ still-face paradigm (Cassel et al. 2007, Merin et al. 2007) • Coding of mother-infant free play interactions (Yirmiya et al. 2006) • The face-to-face/ still-face paradigm (Cassel et al. 2007, Merin et al. 2007)

		<ul style="list-style-type: none"> mouth • Reduced symbolic behaviour during free play • Fewer distal gestures (e.g. pointing) • Fewer conventional gestures • Imitation difficulties • Reduced functional play behaviour 	<ul style="list-style-type: none"> - / + (2) + + (1) - - (1) - - (1) - - (1) 	<ul style="list-style-type: none"> • Communication and Symbolic Behavior Scale Developmental Profile (Toth et al. 2007) • Communication and Symbolic Behavior Scale Developmental Profile (Toth et al. 2007) • Communication and Symbolic Behavior Scale Developmental Profile (Toth et al. 2007) • Battery of imitation tasks (Toth et al. 2007) • Coding of free-play assessment (Christensen et al. 2010)
	4. Repetitive, restrictive behaviours and interests	<ul style="list-style-type: none"> • Higher non-functional repeated behaviours (e.g. banging and chewing on toys) 	<ul style="list-style-type: none"> + + (1) 	<ul style="list-style-type: none"> • Coding of free-play assessment (Christensen et al. 2010)
Cognitive level	5. Social cognition	<ul style="list-style-type: none"> • ‘Theory of Mind’ understanding 	<ul style="list-style-type: none"> - - (1) 	<ul style="list-style-type: none"> • Strange Stories Task (Shaked et al. 2006) • False Belief Task (Shaked et al. 2006)
	6. Executive functioning	<ul style="list-style-type: none"> • Enhanced working memory for non-social targets 	<ul style="list-style-type: none"> + + (1) 	<ul style="list-style-type: none"> • Modified ‘Peekaboo’ Game (Noland et al. 2009)
	7. Visual attention	<ul style="list-style-type: none"> • Attentional disengagement 	<ul style="list-style-type: none"> - / + (2) 	<ul style="list-style-type: none"> • Visual orienting task (Elsabaggh et al. 2009b)
		<ul style="list-style-type: none"> • Difficulties automatically orienting to targets/ forming expectations about visual environment 	<ul style="list-style-type: none"> + + (1) 	<ul style="list-style-type: none"> • Visual orienting task (Elsabaggh et al. 2009b)
		<ul style="list-style-type: none"> • Face processing: increased attention to mouth, relative to eyes 	<ul style="list-style-type: none"> + + (1) 	<ul style="list-style-type: none"> • The face-to-face/ still-face paradigm (Ibanez et al. 2008. Merin et al. 2007)
	8. Language ability	<ul style="list-style-type: none"> • Receptive/ expressive language abilities 	<ul style="list-style-type: none"> + (6) 	<ul style="list-style-type: none"> • The Mullen Scales of Early Learning (Toth et al. 2007) • Clinical Evaluation of Language Fundamentals for pre-school children (Levy and Bar Yuda 2011)
9. Contrast sensitivity	<ul style="list-style-type: none"> • Luminance contrast sensitivity 	<ul style="list-style-type: none"> + + (1) 	<ul style="list-style-type: none"> • Forced-Choice Preferential Looking Paradigm using chromatic and luminance gratings (McCleery et al. 2007) 	
10. General Cognitive abilities	<ul style="list-style-type: none"> • Delays in general cognitive development 	<ul style="list-style-type: none"> - - (5) 	<ul style="list-style-type: none"> • Bayley Scales of Infant Development, 2nd Edition (Yirmiya et al. 2007) 	

*scoring system approximately indicates the percentage of studies reviewed that report statistically significant differences between autism relatives and clinical/ non-clinical control groups

++ = 80-100%

+ = 60-80%

- / + = 40-60%

- = 20-40%

-- = 0-20%

Table 2. Candidate traits constituting the BAP in older relatives.

	Category	Candidate Traits	Support in research literature* (number of studies reviewed)	Measures used (examples)
Behavioural level	1. Language and communication	<ul style="list-style-type: none"> • Pragmatic difficulties • Broadly defined communication difficulties • Structural language problems • Reading/ writing/ spelling and articulation problems • Difficulties engaging in spontaneous narrative discourse 	<p>++ (8)</p> <p>++ (9)</p> <p>- / + (2)</p> <p>- / + (5)</p> <p>++ (1)</p>	<ul style="list-style-type: none"> • Pragmatic Rating Scale (Losh et al. 2008) • Autism Family History Interview (Folstein et al. 1999, Pickles et al. 2000, Piven et al. 1997a) • Children’s Communication Checklist-2 (Bishop et al. 2006) • Autism Family History Interview (Folstein et al. 1999, Pickles et al. 2000, Piven et al. 1997a) • Narrative discourse task (Landa et al. 1991)
	2. Social interaction	<ul style="list-style-type: none"> • Broadly defined social difficulties • Alexithymia • Reduced quality/ number of social relationships • Reduced social motivation • Reduced social expressiveness • Reduced social responsiveness • Poor social skills • Reduced social engagement 	<p>++ (4)</p> <p>++ (1)</p> <p>++ (4)</p> <p>no control groups (1)</p> <p>no control groups (1)</p> <p>++ (2)</p> <p>++ (6)</p> <p>++ (1)</p>	<ul style="list-style-type: none"> • Autism Family History Interview (Folstein et al. 1999, Pickles et al. 2000, Piven et al. 1997a) • Toronto Alexithymia Scale-20 (Szatmari et al. 2008) • The Friendship Interview (Losh and Piven 2007) • Broader Phenotype Autism Symptom Scale (Dawson et al. 2007) • Broader Phenotype Autism Symptom Scale (Dawson et al. 2007) • The Social Responsiveness Scale (Constantino et al. 2006) • Autism-Spectrum Quotient (Bishop et al. 2004) • Communication Checklist – Adult Version (Whitehouse et al. 2010)
	3. Repetitive, restrictive behaviours and interests	<ul style="list-style-type: none"> • Rigidity • Circumscribed interests 	<p>+</p> <p>--</p> <p>(5)</p> <p>(2)</p>	<ul style="list-style-type: none"> • Modified Personality Assessment Schedule-Revised (Losh et al. 2008) • Clinical interview (Wolff et al. 1988)

		<ul style="list-style-type: none"> • Broadly defined stereotyped behaviours • Reports of real-life non-social skills and preferences 	<p>+ (4)</p> <p>++ (1)</p>	<ul style="list-style-type: none"> • Autism Family History Interview (Piven et al. 1997a) • Real life styles and preferences questionnaire (Briskman et al. 2001)
Cognitive level	4. Social cognition	<ul style="list-style-type: none"> • Theory of Mind ability • Emotion recognition • Trustworthiness of faces • Discerning emotional content of complex social scenes • Differences in face processing strategy • Face recognition/ memory ability • Eye gaze processing/ social orienting difficulties 	<p>+ (7)</p> <p>+ (7)</p> <p>++ (1)</p> <p>++ (1)</p> <p>++ (1)</p> <p>- / + (4)</p> <p>++ (2)</p>	<ul style="list-style-type: none"> • The Mind in Eyes Test (Baron-Cohen and Hammer 1997) • Emotion Recognition Test (Bölte and Poustka 2003) • Trustworthiness of Faces Task (Losh et al. 2009) • Movie Stills Task (Losh et al. 2009) • ‘Pictures of Facial affect’/ ‘Bubbles’ Task (Adolphs et al. 2008) • Facial Recognition Task (Dalton et al. 2007) • Directional Judgement Task (Wallace et al. 2010)
	5. Executive Function and visuospatial memory	<ul style="list-style-type: none"> • Mental flexibility/ set-shifting • Reduced planning ability • Ideational Fluency • Verbal fluency • Design fluency • ‘Association fluency’ • Inhibition/ working memory problems (verbal/ spatial) • Spatial span 	<p>- (9)</p> <p>- / + (9)</p> <p>++ (1)</p> <p>- (5)</p> <p>- / + (2)</p> <p>-- (1)</p> <p>- (6)</p> <p>+ (3)</p>	<ul style="list-style-type: none"> • Wisconsin Card Sorting Test (Bölte and Poustka 2006) • Tower of Hanoi (Losh et al. 2009) • Pattern meanings (Wong et al. 2006) • FAS Verbal Fluency Task (Hughes et al. 1999) • The Design Fluency Task (Delorme et al. 2007) • The Association Fluency Task (Delorme et al. 2007) • Delayed Oculomotor Response Task (Koczat et al. 2002) • Spatial span task (Hughes et al. 1999)
	6. Visual attention, sensory integration and sensorimotor functioning	<ul style="list-style-type: none"> • local attentional biases/ ‘weak central coherence’ • Susceptibility to visual illusion • ‘Complex’ divided, selective attention/ selective inhibition • Attentional engagement/ disengagement 	<p>- / + (6)</p> <p>++ (1)</p> <p>++ (1)</p> <p>++ (1)</p>	<ul style="list-style-type: none"> • Embedded Figures Task (Happé et al. 2001) • Titchener Circles Illusion (Happé et al. 2001) • Visual, divided attention task (Belmonte et al. 2010) • The Detection Task (Scheeren and Stauder 2008)

		<ul style="list-style-type: none"> Oculomotor abnormalities (e.g. open-loop pursuit gain) 	++ (1)	<ul style="list-style-type: none"> Saccade and foveofugal step-ramp tasks (Mosconi et al. 2010)
	7. Language ability	<ul style="list-style-type: none"> Phonological Processing Rapid Automatised Naming (RAN) Receptive and expressive language ability Reading ability Spelling ability 	<p>- (3)</p> <p>- / + (4)</p> <p>-- (3)</p> <p>+ (5)</p> <p>- / + (5)</p>	<ul style="list-style-type: none"> The Comprehensive Test of Phonological Processing (Lindgren et al. 2009) Object and Colour naming tasks (Losh et al. 2010) The Clinical Evaluation of Language Fundamentals, 3rd Edition (Lindgren et al. 2009, Pilowsky et al. 2003) The Woodcock-Johnson Psycho-Educational Battery-Revised (Lindgren et al. 2009) The Schonell Graded Word Spelling Test-B (Fombonne et al. 1997)
	8. Motion Perception	<ul style="list-style-type: none"> Luminance contrast sensitivity/ 'atypical Magnocellular pathway functioning' 	- / + (2)	<ul style="list-style-type: none"> Detection and Motion Tasks (Koh et al. 2010)
	9. General Cognitive abilities	<ul style="list-style-type: none"> Intellectual functioning/ disability 	- / + (12)	<ul style="list-style-type: none"> WAIS-R/ WISC-R (Fombonne et al. 1997)
Psychiatric history	10. Other Psychiatric Conditions	<ul style="list-style-type: none"> Depression/ affective disorder Social phobia Anxiety disorder Obsessive Compulsive Disorder Motor tics Schizophrenia Alcoholism 	<p>++ (10)</p> <p>++ (2)</p> <p>+ (4)</p> <p>++ (6)</p> <p>- / + (2)</p> <p>-- (2)</p> <p>-- (2)</p>	<ul style="list-style-type: none"> The Maudsley SADS-L (Bolton et al. 1998) Schedule for Affective Disorders and Schizophrenia (Piven and Palmer 1999) Self-report and GP medical records on family psychiatric history (Micali et al. 2004) Autism Family History Interview (Bolton et al. 1998) Autism Family History Interview (Bolton et al. 1998) Autism Family History Interview (Ghaziuddin 2005) Autism Family History Interview (Piven and Palmer 1999)
Personality Traits	11. Personality Traits	<ul style="list-style-type: none"> Rigid Impulsive Aloof 	<p>+ (5)</p> <p>- / + (2)</p> <p>++ (5)</p>	<ul style="list-style-type: none"> The Modified Personality Assessment Schedule-Revised (Losh et al. 2008, 2009, Murphy et al. 2000) The Modified Personality Assessment Schedule-Revised (Losh et al. 2008, 2009, Murphy et al. 2000) The Modified Personality Assessment Schedule-Revised

		<ul style="list-style-type: none"> • Shy • Untactful • Schizoid/ reserved • Irritable • Hypersensitive • Neuroticism • Undemonstrative • Anxious • Conscientious 	<p>- / + (2)</p> <p>- / + (4)</p> <p>+ + (2)</p> <p>- / + (2)</p> <p>+ (5)</p> <p>+ + (2)</p> <p>- (3)</p> <p>+ (4)</p> <p>- (5)</p>	<p>(Losh et al. 2008, 2009, Murphy et al. 2000)</p> <ul style="list-style-type: none"> • The Modified Personality Assessment Schedule-Revised (Losh et al. 2008, 2009, Murphy et al. 2000) • The Modified Personality Assessment Schedule-Revised (Losh et al. 2008, 2009, Murphy et al. 2000) • Personality Style and Disorder Inventory (Bölte et al. 2007) • The Modified Personality Assessment Schedule-Revised (Piven et al. 1994) • The Modified Personality Assessment Schedule-Revised (Piven et al. 1994) • The NEO personality inventory (Losh et al. 2008) • The Modified Personality Assessment Schedule-Revised (Piven et al. 1994) • The Modified Personality Assessment Schedule-Revised (Piven et al. 1994) • The Modified Personality Assessment Schedule-Revised (Piven et al. 1994)
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*scoring system approximately indicates the percentage of studies reviewed that report statistically significant differences between autism relatives and clinical/ non-clinical control groups

- + + = 80-100%
- + = 60-80%
- / + = 40-60%
- = 20-40%
- - = 0-20%

Table 3. *Neurofunctional and neurostructural atypicalities linked to the aetiology of the BAP. Only a small number of neuroimaging studies have currently been carried out on the relatives of autistic probands*

Type of neuroimaging study	Brain Region(s) affected	Functional or Structural Atypicality	Task	Relative(s) studied	Study
1. fMRI	Left medial Temporal Gyrus, Inferior Frontal Gyrus	Hypoactive	The Mind in Eyes test	Parents	Baron-Cohen et al. (2006)
	Temporal Poles, right middle/ left posterior Superior Temporal Sulcus, right Fusiform Face Area, left superior Frontal Gyrus, left dorsomedial prefrontal cortex.	Hypoactive	Facial Emotion Processing Task (Happy vs. Neutral)	Siblings	Spencer et al. (2011)
	Fusiform Gyrus	Hypoactive	Facial Recognition task	Siblings	Dalton et al. (2007)
	Fusiform Gyrus, Left dorsolateral prefrontal cortex, Right inferior Temporal Gyrus	Hypoactive	Biological motion task	Siblings	Kaiser et al. (2010)
	Extra striate cortex: left lingual gyrus and right middle occipital gyrus	Hypoactive	The Embedded Figures task	Parents	Baron-Cohen et al. (2006)
	Fronto-cerebellar complex	Delayed activation	Visual 'divided attention' task	Siblings	Belmonte et al. (2010)
2. Near-infrared spectroscopy	Anterior Prefrontal cortex	Changes in [oxy-Hb] intermediate between autism and controls	Verbal fluency task	Siblings	Kawakubo et al. (2009)
3. ERP	Inferior right and left posterior temporal electrodes	Shorter latency N170 to faces vs. Objects/ No right-hemisphere lateralised ERP pattern to faces	Face recognition sub-tests from WMS-III and Woodcock Johnson Object Recognition Subtest	Parents	Dawson et al. (2005)
	Anterior central, left and right temporal and posterior electrodes	Prolonged latency in 'P-400' ERP component in response to direct gaze	Direct vs. Averted Gaze Task using static face stimuli	'At-risk' infant siblings	Elsabaggh et al. (2009)
4. MEG	N/A	Increased induced gamma-band power at 40Hz/ reduced evoked gamma-band	Presentation of auditory (pure-tone) stimuli	Parents	Rojas et al. (2008)

		power/ phase-locking factor			
	N/A	Reduced gamma-band phase locking factor and phase-locked power	Presentation of auditory stimuli: 30/40/48 Hz amplitude-modulated sounds	Parents	Rojas et al. (2011)
5. sMRI	Amygdala	Smaller volume	N/A	Siblings	Dalton et al. (2007)
	Left Hippocampus	Larger volume	N/A	Parents	Rojas et al. (2004)
	Inferior/ medial Frontal Gyri and cerebellum	Significant increases in gray matter	N/A	Parents	Peterson et al. (2006)
6. DTI	Temporo-parietal junctions, medial prefrontal and superior temporal regions	Significantly reduced white matter/ axial diffusivity	N/A	Siblings	Barnea-Goraly et al. (2010)