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Autism spectrum conditions

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1. Autism Spectrum Conditions

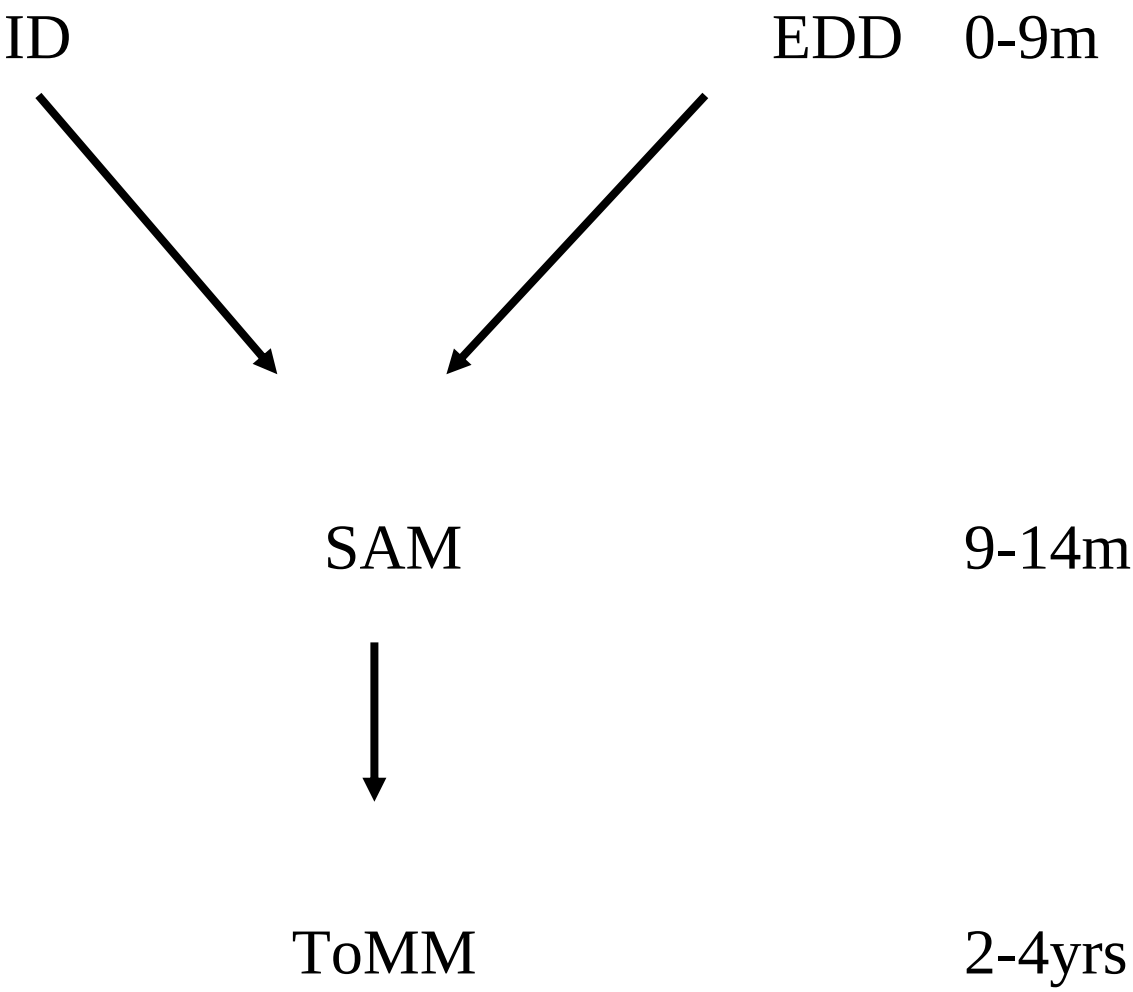
Autism is diagnosed when a child or adult has abnormalities in a 'triad' of behavioural domains: social development, communication, and repetitive behaviour/obsessive interests (A.P.A, 1994; I.C.D-10, 1994). Autism can occur at any point on the IQ continuum, and IQ is a strong predictor of outcome (Rutter, 1978). Autism is also invariably accompanied by language delay (no single words before 2 years old). Asperger Syndrome (AS) (Asperger, 1944) is a subgroup on the autistic spectrum. People with AS share many of the same features as are seen in autism, but with no history of language delay and where IQ is in the average range or above. In this chapter we will use the term autism spectrum conditions (ASC) to describe the whole spectrum of individuals who meet diagnostic criteria for one or other of these subgroups. Because autism is a developmental condition, we will at times be discussing adults with this diagnosis, even though this book has a focus on child psychiatry. Adult studies are of course relevant not only because the onset of ASC is during early childhood, but also because of how changes across the lifespan throw light on developmental outcomes.

2. Typical development of mindreading

In 1994 Baron-Cohen proposed a model to specify the neurocognitive mechanisms that comprise the 'mindreading system' (Baron-Cohen, 1994, , 1995). Mindreading is defined

as the ability to interpret one's own or another agent's actions as driven by mental states. The model was proposed in order to explain (a) ontogenesis of a theory of mind, and (b) neurocognitive dissociations that are seen in children with or without autism. The model is shown in Figure 1 and contains four components: ID, or the Intentionality Detector. EDD, or the Eye Direction Detector. SAM, or the Shared Attention Mechanism. And finally ToMM, or the Theory of Mind Mechanism.

Figure 1: Baron-Cohen's (1994) model of mindreading



Key: IDD = Intentionality Detector
EDD = Eye Direction Detector
SAM = Shared Attention Mechanism
ToMM = Theory of Mind Mechanism

ID and EDD build 'dyadic' representations of simple mental states. ID automatically interprets or represents an agent's self-propelled movement as a desire or goal-directed movement, a sign of its agency, or an entity with volition (Premack, 1990). For example, ID interprets an animate-like moving shape as "it wants x", or "it has goal y". EDD automatically interprets or represents eye-like stimuli as "looking at me" or "looking at something else". That is, EDD picks out that an entity with eyes can perceive. Both ID and EDD are developmentally prior to the other two mechanisms, and are active early in infancy.

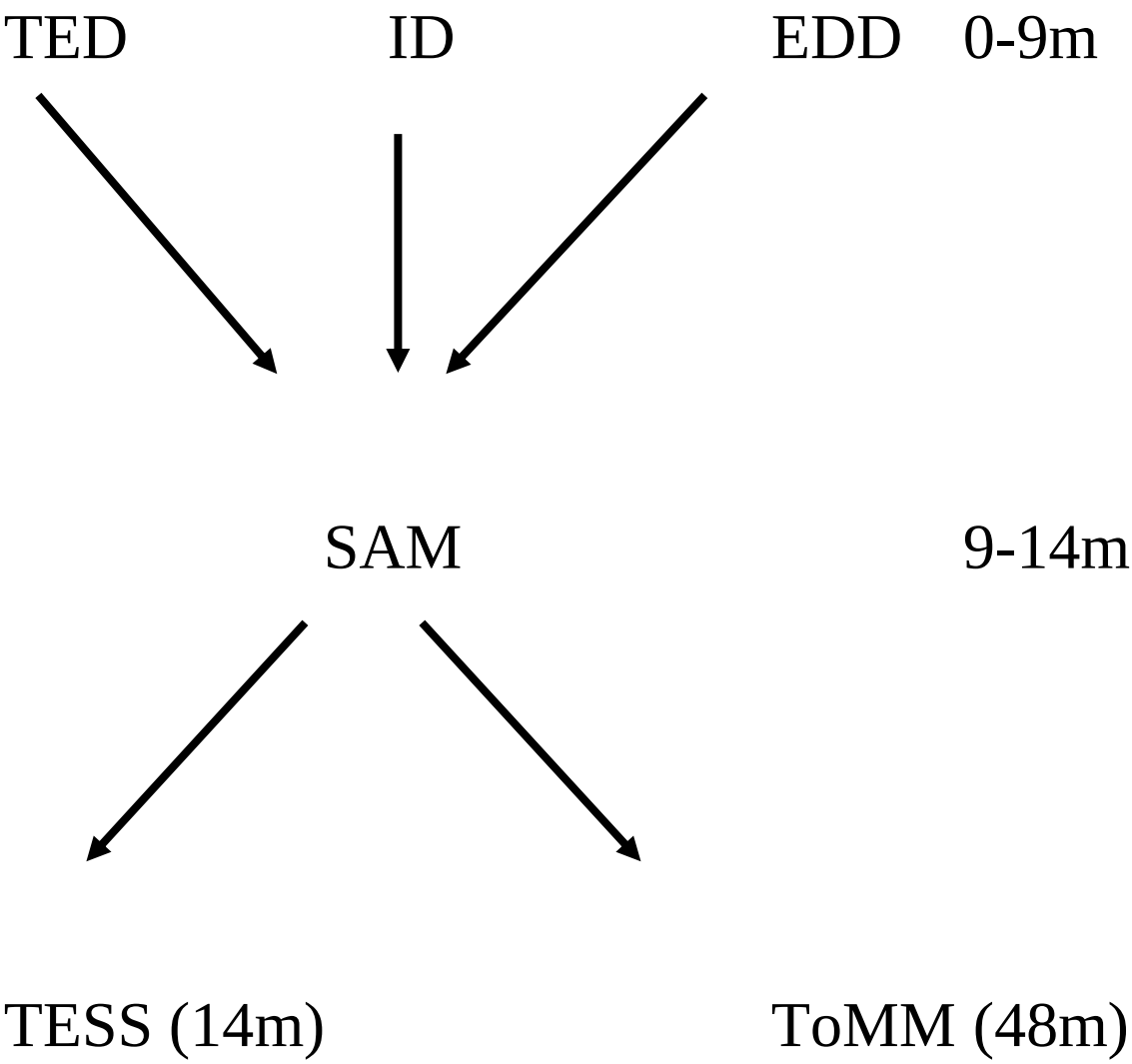
SAM is developmentally more advanced and comes on line at the end of the first year of life. SAM automatically interprets or represents if the self and another agent are perceiving the same event. SAM does this by building 'triadic' representations. For example, where ID can build the dyadic representation 'Mother wants the cup' and where EDD can build the dyadic representation 'Mother sees the cup', SAM can build the triadic representation 'Mother sees that I see the cup'. As is apparent, triadic representations involve embedding or recursion. (A dyadic representation ("I see a cup") is embedded within another dyadic representation ("Mum sees the cup") to produce this triadic representation). SAM takes its input from ID and EDD, and triadic representations are made out of dyadic representations. SAM typically functions from 9-14 months of age, and allows 'joint attention' behaviours such as protodeclarative pointing and gaze monitoring (Scaife & Bruner, 1975).

ToMM allows epistemic mental states to be represented (e.g., 'Mother thinks this cup contains water' or 'Mother pretends this cup contains water'), and it integrates the full set of mental state concepts (including emotions) into a theory. ToMM develops between 2 and 4 years of age, and allows pretend play (Leslie, 1987), understanding of false belief (Wimmer & Perner, 1983), and understanding of the relationships between mental states (Wellman, 1990). An example of the latter is the seeing-leads-to-knowing principle (Pratt & Bryant, 1990), where the typical 3 year old can infer that if someone has seen an event, then they will know about it.

The model shows the ontogenesis of a theory of mind in the first four years of life, and justifies the existence of four components on the basis of developmental competence and neuropsychological dissociation. In terms of developmental competence, joint attention does not appear possible until 9-14 months of age, and joint attention appears to be a necessary but not sufficient condition for understanding epistemic mental states (Baron-Cohen, 1991; Baron-Cohen & Swettenham, 1996). There appears to be a developmental lag between acquiring SAM and ToMM, suggesting that these two mechanisms are dissociable. In terms of neuropsychological dissociation, congenitally blind children can ultimately develop joint (auditory or tactile) attention, using the amodal ID rather than the visual EDD route. Children with autism appear able to represent the dyadic mental states of seeing and wanting, but show delays in shared attention (Baron-Cohen, 1989b) and in understanding false belief (Baron-Cohen, 1989a; Baron-Cohen et al., 1985) – that is, in acquiring SAM and ultimately ToMM. It is this specific developmental delay that suggests that SAM is dissociable from EDD.

The 1994 model of the Mindreading System was revised in 2005 because of certain omissions and too narrow a focus. The key omission is that information about affective states, available to the infant perceptual system, has no dedicated neurocognitive mechanism. In Figure 2, the revised model (Baron-Cohen, 2005) is shown and now includes a new fifth component: TED, or The Emotion Detector. But the concept of mindreading (or theory of mind) makes no reference to the affective state in the observer triggered by recognition of another's mental state. This is a particular problem for any account of the distinction between autism and psychopathy. For this reason, the model is no longer of 'mindreading' but is of 'empathizing', and the revised model also includes a new sixth component, TESS, or The Empathizing SyStem. Where the 1994 Mindreading System was a model of a passive observer (because all the components had simple decoding functions), the 2005 Empathizing System is a model of an observer impelled towards action (because an emotion is triggered in the observer which typically motivates the observer to respond to the other person).

Figure 2: Baron-Cohen's (2005) model of empathizing



Key: As in Figure 1, but:
TED = The Emotion Detector; and
TESS = The Empathising SyStem

Like the other infancy perceptual input mechanisms of ID and EDD, the new component of TED can build dyadic representations of a special kind, namely, it can represent affective states. An example would be 'Mother - is unhappy', or even 'Mother - is angry - with me'. Formally, we can describe this as Agent-affective state-proposition. We know that infants can represent affective states from as early as 3 months of age (Walker, 1982). As with ID, TED is amodal, in that affective information can be picked up from facial expression, or vocal intonation, 'motherese' being a particularly rich source of the latter (Field, 1979). Another's affective state is presumably also detectable from their touch (e.g., tense, vs. relaxed), which implies that congenitally blind infants should find affective information accessible through both auditory and tactile modalities. TED allows the detection of the basic emotions (Ekman & Friesen, 1969). The development of TED is probably aided by simple imitation that is typical of infants (e.g., imitating caregiver's expressions) which in itself would facilitate emotional contagion (Meltzoff & Decety, 2003).

When SAM becomes available, at 9-14 months of age, it can receive inputs from any of the 3 infancy mechanisms, ID, EDD, or TED. Here, we focus on how a dyadic representation of an affective state can be converted into a triadic representation by SAM. An example would be that the dyadic representation 'Mother is unhappy' can be converted into a triadic representation 'I am unhappy that Mother is unhappy', or 'Mother is unhappy that I am unhappy', etc. Again, as with perceptual or volitional states, SAM's triadic representations of affective states have this special embedded, or recursive property. The phenomenon of social referencing, in which toddlers approach objects

towards which their caregiver looks at approvingly, or avoid those objects towards which the caregiver shows alarm or disapproval, is one index of SAM (Klinnert, 1984).

ToMM has been celebrated for the last 20 years in research in developmental psychology (Leslie, 1987; Whiten, 1991; Wimmer et al., 1988) . ToMM is of major importance in allowing the child to represent the full range of mental states, including epistemic ones (such as false belief), and is important in allowing the child to pull mentalistic knowledge into a useful theory with which to predict behaviour (Baron-Cohen, 1995; Wellman, 1990). But TESS allows more than behavioural explanation and prediction (itself a powerful achievement). TESS allows an empathic reaction to another's emotional state. This is however, not to say that these two modules do not interact. Knowledge of mental states of others made possible by TOMM could certainly influence the way in which an emotion is processed and/or expressed by TESS. TESS also allows for sympathy. It is this element of TESS that gives it the adaptive benefit of ensuring that organisms feel a drive to help each other, seen in a toddler's early comforting behaviour towards those in distress (Harris, 1989).

To see the difference between TESS and ToMM, consider this example: I see you are in pain. Here, ToMM is needed, to interpret your facial expressions and writhing body movements in terms of your underlying mental state (pain). But now consider this further example: I am devastated - that you are in pain. Here, TESS is needed, since an appropriate affective state has been triggered in the observer by the emotional state

identified in the other person. And where ToMM employs M-Representations (Leslie, 1995) of the form Agent-attitude-proposition (e.g., Mother – believes - Johnny – took-the - cookie), TESS employs a new class of representations, which we can all E-Representations of the form Self-Affective state-[Self-Affective state-proposition] (e.g 'I feel sorry that – Mom feels sad about – the news in the letter') (Baron-Cohen, 2003). The critical feature of this E-Representation is that the self's affective state is appropriate to and triggered by the other person's affective state. Thus, TESS can represent [I am horrified - that you are in pain], or [I am concerned - that you are in pain], or [I want to alleviate- that you are in pain], but it cannot represent [I am happy – that you are in pain]. At least, it cannot do so if TESS is functioning normally. One could imagine an abnormality in TESS leading to such inappropriate emotional states being triggered, or one could imagine them arising from other systems (such as a competition system, or a sibling-rivalry system), but these would not be evidence of TESS per se.

Before moving to review the development of mindreading in autism spectrum conditions we should mention the literature documenting typical sex differences in empathizing, with females showing greater attention to faces at birth (Connellan et al., 2001), more eye contact as toddlers (Lutchmaya et al., 2002), greater sensitivity to faux pas in childhood (Baron-Cohen, O'Riordan et al., 1999), and better ability to decode subtle mental states from facial expressions (Baron-Cohen et al., 1997). Such sex differences are one clear source of evidence for individual differences in empathy. Taking a dimensional approach to empathy as a normally distributed trait in the population leads to the view that autism spectrum conditions may simply be at one end of a spectrum that runs throughout the

population. (We do not suppose that this is the only relevant dimension along which individuals with autism differ, another one being in 'systemizing', but that literature is reviewed elsewhere (Baron-Cohen, 2002, , 2006; Goldenfeld et al., in press).

3. Mindreading in Autism Spectrum Conditions

Since the first test of mindblindness in children with autism (Baron-Cohen, Leslie, & Frith, 1985), there have been more than 30 experimental tests. The vast majority of these have revealed profound impairments in the development of their empathizing ability. These are reviewed elsewhere (Baron-Cohen, 1995; Baron-Cohen, Tager-Flusberg et al., 1993). Some children and adults with AS only show their empathizing deficits on age-appropriate tests (Baron-Cohen, Jolliffe, Mortimore et al., 1997; Baron-Cohen, S. et al., 2001; Baron-Cohen, S. et al., 1997). This deficit in their empathizing is thought to underlie the difficulties such children have in social and communicative development (Baron-Cohen, 1988; Tager-Flusberg, 1993), and in the imagination of others' minds (Baron-Cohen, 1987; Leslie, 1987).

The majority of studies of emotion recognition have focused on the face and tested recognition of 6 emotions (happiness, sadness, fear, anger, surprise and disgust). These 'basic emotions' are expressed and recognized universally (Ekman, 1993; Ekman & Friesen, 1971). Some studies reveal emotion recognition deficits among individuals with ASC, compared to typical or clinical control groups, using both static (Celani et al., 1999; Deruelle et al., 2004; MacDonald et al., 1989) and dynamic stimuli (Hobson, R P, 1986;

Hobson, R.P., 1986; Yirmiya et al., 1992). Other studies have found children and adults with high-functioning autism (HFA) or Asperger Syndrome (AS) have no difficulties in recognizing these basic emotions from pictures (Adolphs et al., 2001; Grossman et al., 2000) or films (Loveland et al., 1997). Possible reasons for this apparent lack of consistency is the heterogeneity of symptom severity within the ASC population and the fact that accuracy measures for emotion recognition tasks might not be fine-tuned to pick up subtle differences in measures of perceived task difficulty, e.g. reaction time. Correlative designs in future experiments, with quantitative dimensions of 'symptom' severity, such as the ADI-R (Lord et al., 1994) or AQ (Baron-Cohen, S et al., 2001) should hopefully resolve this issue. The observed deficit in accuracy measures of emotion recognition becomes much more apparent when testing recognition of more 'complex' emotions (such as embarrassment, insincerity, intimacy, etc) in both adults and children with ASC (Baron-Cohen, Wheelwright, Hill et al., 2001; Baron-Cohen, Wheelwright, & Jolliffe, 1997; Golan, Baron- Cohen, & Hill, 2006). These findings suggest recognition of basic emotions is relatively preserved among high functioning individuals with ASC, and that they show greater difficulties recognizing more complex emotional and mental states.

Emotion recognition from voices has been studied less frequently. Here too there are contradictory findings in relation to recognition of basic emotions (Boucher et al., 2000; Loveland et al., 1995; Loveland, Tunali Kotoski, Chen et al., 1997). Regarding recognition of complex emotions from voices, several studies report a deficit in performance in high-functioning adults with ASC compared to controls (Golan, Baron-

Cohen, & Hill, 2006; Golan, Baron-Cohen, Hill, & Rutherford, submitted; Kleinman et al., 2001; Rutherford et al., 2002).

Studies assessing the ability of individuals with ASC to identify emotions and mental states from context have also shown deficits relative to the general population or to other clinical control groups (Baron-Cohen et al., 1986; Fein et al., 1992). For example, adolescents and adults with ASC have difficulties answering questions on the Strange Stories Test (Happe, 1994; Jolliffe & Baron-Cohen, 1999). This test assesses the ability to provide context-appropriate mental state explanations for non-literal statements made by story characters (e.g., ironic or sarcastic statements).

Studies assessing complex emotion and mental state recognition from ecologically rich social situations, containing multimodal sources of information, show a deficit in individuals with ASC, compared to controls (Golan, Baron-Cohen, Hill, & Golan, submitted; Heavey et al., 2000; Klin et al., 2002). These difficulties may be related to a failure to attend to the right emotional cues, and/or to a failure integrating them, explained by weak central coherence in the cognitive level (Frith, 1989), and under-connectivity between brain regions in the neurobiological level (Belmonte, Allen et al., 2004; Belmonte, Cook, Anderson et al., 2004; Courchesne & Pierce, 2005; Critchley, H. et al., 2000).

To summarize, although emotion recognition deficits in ASC are life-long, some high-functioning individuals develop compensatory strategies that allow them to recognize

basic emotions. However, when recognition of more complex emotions and mental states is required, either from faces, voices, context, or the integration of these, many find them hard to interpret. It would appear that in autism TED may function, although this may be delayed (Baron-Cohen, Spitz et al., 1993; Baron-Cohen, Wheelwright, & Jolliffe, 1997; Hobson, R.P., 1986), at least in terms of detecting basic emotions. Even high-functioning people with autism or Asperger Syndrome have difficulties both in ToMM (when measured with mental-age appropriate tests) (Baron-Cohen, Jolliffe, Mortimore et al., 1997; Baron-Cohen, Wheelwright, Hill et al., 2001; Happe, 1994) and TESS (Attwood, 1997; Baron-Cohen, O'Riordan, Jones et al., 1999; Baron-Cohen et al., 2003; Baron-Cohen & Wheelwright, 2004; Baron-Cohen, Wheelwright et al., 1999; Dapretto et al., 2006)**.** This suggests TED and TESS may be fractionated.

In contrast, the psychiatric condition of psychopathy may entail an intact TED and ToMM, alongside an impaired TESS. The psychopath (or sociopath) can represent that you are in pain, or that you believe - that he is the gas-man, thereby gaining access to your house or your credit card. The psychopath can go on to hurt you or cheat you without having the appropriate affective reaction to your affective state. In other words, he or she doesn't care about your affective state (Blair et al., 1997; Mealey, 1995). Lack of guilt or shame or compassion in the presence of another's distress are diagnostic of psychopathy (Cleckley, 1977; Hare et al., 1990). Separating TESS and ToMM thus allows a functional distinction to be drawn between the neurocognitive causes of autism and psychopathy.

4. Causes

We can think of causes of the social cognitive deficits in ASC in terms of the brain basis of empathy and mindreading in the typical brain. This is reviewed first.

Neuroimaging experiments have implicated the following different brain areas for performing tasks that tap empathy. Traditional 'theory of mind' (cognitive empathy) tasks have consistently shown activity in medial prefrontal cortex, superior temporal gyrus and the temporo-parietal junctions (Frith & Frith, 2003; Saxe et al., 2004). This could be equated to the brain basis of ToMM. Studies of emotional contagion have demonstrated involuntary facial mimicry (Dimberg et al., 2000) as well as activity in regions of the brain where the existence of 'mirror' neurons has been suggested (Decety & Jackson, 2004; Keysers & Perrett, 2004; Wicker & al, 2003). Sympathy has been relatively less investigated, with one study implicating the left inferior frontal gyrus, among a network of other structures (Decety & Chaminade, 2003).

ID has been tested in a PET study in a task involving attribution of intentions to cartoon characters (Brunet et al., 2000). Reported activation clusters included the right medial prefrontal (BA 9), inferior frontal (BA 47) cortices, superior temporal gyrus (BA42) and bilateral anterior cingulate cortex. In an elegant set of experiments that required participants to attribute intentions to animations of simple geometric shapes it was found that the 'intentionality' score attributed by the participants to individual animations was positively correlated to the activity in STS, the temporo-parietal junction and the medial

prefrontal cortex (Castelli et al., 2000). In a subsequent study (Castelli et al., 2002), they demonstrated a group difference in activity in the same set of structures between people with Autism/Asperger's Syndrome and neurotypical controls.

EDD has been studied in several neuroimaging studies on gaze direction perception (Calder et al., 2002; Pelphrey et al., 2003), and have implicated the posterior superior temporal sulcus (STS) bilaterally. This evidence, taken together with similar findings from primate literature (Perrett & Emery, 1994) suggests this area to be a strong candidate for the anatomical equivalent of the EDD. This fits in with the Haxby model of face processing, where he suggested the role of this region in processing 'variable' aspects of faces (in contrast to non-varying aspects like identity) (Haxby et al., 2000). A recent imaging study (Williams et al., 2005) investigated the neural correlates of SAM and reported bilateral activation in anterior cingulate (BA 32, 24), and medial prefrontal cortex (BA 9,10) and the body of caudate nucleus in a joint attention task, when compared to a control task involving non-joint attention (Frith & Frith, 2003).

We can now turn to neuroimaging studies of processing facial expressions of emotion in people with ASC. These show less activation in brain regions central to face processing, such as the fusiform gyrus (Critchley, H. D. et al., 2000; Pierce et al., 2001; Schultz et al., 2003). Behavioural studies show that children and adults with ASCs process faces differently compared to controls: Participants with ASC tend to process faces in a feature-based approach, whereas controls process faces configurally (Hobson et al., 1988; Schultz, Grelotti, Klin et al., 2003; Teunisse & De Gelder, 1994; Young & Bruce, 1998).

There is also evidence of reduced activation in brain areas that play a major role in processing of emotion, such as the amygdala, when individuals with ASC process social-emotional information, (Ashwin et al., submitted ; Baron-Cohen, Ring et al., 1999; Critchley, Daly, Phillips et al., 2000).

However, a recent study (Dalton et al., 2005) shows that the observed hypoactivation of the amygdala and the fusiform gyrus in response to facial expressions of emotion is related to the lack of fixation on the eye region of the face. In light of this new result, it is essential to re-evaluate existing results from studies that involve emotional stimuli in a non-visual domain. One study measured brain activity of participants with ASC and matched controls whilst listening to theory of mind stories. Activation in the medial frontal area of the brain, whilst judging others' mental states, was less intensive and extensive in the AS group, compared to controls (Neiminen-von Wendt et al., 2003). When using a verbal ToM task in a neuroimaging study, reduced activation of the left medial prefrontal cortex was found in people with ASC compared to matched controls (Happe & Frith, 1996).

Anatomical abnormalities have been identified in many brain areas in autism. These include the cerebellum (Courchesne, Townsend, Akshoomof et al., 1994; Courchesne, Townsend, & Saitoh, 1994; Hashimoto et al., 1995; Murakami et al., 1989), the brain stem (Hashimoto, Tayama, Murakawa et al., 1995; Rodier et al., 1996), frontal lobes (Aylward et al., 2002; Carper & Courchesne, 2000; Courchesne et al., 2001; Sparks et al., 2002), parietal lobes (Courchesne et al., 1993), hippocampus (Aylward et al., 1999;

Saitoh et al., 2001), and the amygdala (Aylward, Minshew, Goldstein et al., 1999). Volume deficits have been shown in the cerebellum (Courchesne, Townsend, & Saitoh, 1994; Courchesne et al., 1988; Hashimoto, Tayama, Murakawa et al., 1995; Murakami, Courchesne, Press et al., 1989). However, there has been a report of a subgroup of children with ASCs who have an increased cerebellar volume (Courchesne, Saitoh et al., 1994). Epilepsy also occurs commonly, at least in classic autism (Ballaban-Gil & Tuchman, 2000).

In terms of neuropathology, the number of Purkinje cells in the cerebellar cortex is abnormally low (Bauman & Kempner, 1985; Bauman & Kemper, 1994; Ritvo et al., 1986; Williams et al., 1980). This has been postulated to lead to disinhibition of the cerebellar deep nuclei and consequent over-excitement of the thalamus and cerebral cortex (Courchesne, Townsend, Akshoomof et al., 1994)**.** The brainstem (Hashimoto, Tayama, Murakawa et al., 1995), and posterior corpus callosum (Egaas et al., 1995) have also been shown to have lower volumes in people with ASCs when compared to neurotypical controls. A volume deficit has also been reported in the parietal lobe (Courchesne, Press, & Yeung-Courchesne, 1993). Neuropsychology suggests this is associated with a narrowed spatial focus of attention (Townsend & Courchesne, 1994). Using either MRI volumetric analysis, or measures of head circumference, the autistic brain appears to involve transient postnatal macroencephaly (Courchesne, 2002). Neonates later diagnosed with autism or PDD-NOS (Pervasive Developmental Disorder-Not Otherwise Specified) have normal head circumference, but by 2-4 years of age 90% of these have MRI-based brain volumes larger than average (Carper & Courchesne, 2000;

Courchesne, Karns, Davis et al., 2001); (Aylward, Minshew, Field et al., 2002; Sparks, Friedman, Shaw et al., 2002). This reflects an enlargement of cerebellar and cerebral white matter, and cerebral grey matter (Courchesne, Karns, Davis et al., 2001; Herbert et al., 2003). Enlargement of superficial white matter tracts containing cortico-cortical fibres may persist abnormally late into development, whilst the internal capsule and corpus callosum are smaller (Herbert et al., 2002). Cerebellar and cerebral white matter volumes, and cerebellar vermis size, can distinguish 95% of toddlers with autism from normal controls, and predict if the child with autism will be high or low functioning (Courchesne, Karns, Davis et al., 2001). The *overgrowth* is anterior-to-posterior (frontal lobes being the largest). This increase in volume of cortical grey matter may reflect a failure of synaptic pruning, or an excess of synaptogenesis (Belmonte, Allen, Beckel-Mitchener et al., 2004).

Abnormalities in the density of packing of neurons in the hippocampus, amygdala, and other parts of the limbic system have also been reported (Bauman & Kempner, 1985; Bauman & Kemper, 1994; Raymond et al., 1996). An abnormally low degree of dendritic branching was also found in a Golgi analysis of the hippocampus of two autistic brains (Raymond, Bauman, & Kemper, 1996), though it remains to be seen if such an abnormality is confirmed in a larger sample. A separate report suggests a reduction in the size of cortical minicolumns and an increase in cell dispersion within these minicolumns. These might indicate an increase in the number of and connectivity between minicolumns (Casanova, M., F, et al., 2002; Casanova, M. F. et al., 2002).

Abnormal levels of arousal have been inferred from physiological and endocrine indexes (Hirstein et al., 2001; Tordjman et al., 1997). Functional studies suggest that sensory inputs evoke hyper-activation, resulting in decreased ability to select amongst competing inputs. Thus, on the Embedded Figures Task, people with autism show unusually high activation in ventral occipital areas and abnormally low activation in prefrontal and parietal areas (Ring et al., 1999).

Regarding ERP results, the P1 evoked potential is either abnormally heightened in response to stimuli that are the target of attention, or abnormally generalized to stimuli that are outside the target of attention (Townsend & Courchesne, 1994). The visual N2 to novel stimuli is also heightened to irrelevant stimuli (Kemner et al., 1994). The P3 in response to auditory stimuli is abnormally generalized to occipital sites in visual cortex (Kemner et al., 1995). Both hemispheres show abnormal activation – indiscriminately - during shifts of attention into either hemifield (Belmonte, 2000; Belmonte & Yurgelun-Todd, 2003). Regarding attentional research, a deficit has been found in rapid shifting of attention between modalities (Courchesne, Townsend, Akshoomof et al., 1994), between spatial locations (Belmonte, 2000; Harris et al., 1999; Townsend et al., 1999; Townsend, Courchesne et al., 1996; Townsend, Singer-Harris et al., 1996; Wainwright-Sharp & Bryson, 1993, , 1996) and between object features (Courchesne, Townsend, Akshoomoff et al., 1994; Rinehart et al., 2001).

A neural basis of empathy has built on a model first proposed by Brothers (Brothers, 1990). She suggested from both animal lesion studies (Kling & Brothers, 1992), single cell recording studies (Brothers et al., 1990), and neurological studies that social intelligence was a function of three regions: the amygdala, the orbito-frontal and medial frontal cortex, and the superior temporal sulcus and gyrus (STG). Together, she called these the "social brain". Abnormalities in autism have been found in the amygdala, the orbito- and the medial-frontal cortex.

There is converging evidence from several lines of research on the abnormalities of this 'social brain' structures in ASCs. There is evidence for amygdala hypoactivation in an emotion recognition task in autism (Baron-Cohen et al., 2000). We have reported significantly less amygdala activation in adults with High Functioning Autism/Asperger's Syndrome during a mentalizing task (Reading the Mind in the Eyes task), compared to normal (Baron-Cohen, Ring, Wheelwright et al., 1999). Reduced activity in these 'social brain' structures has been reported in the left medial frontal cortex (Happe et al., 1996), during an empathizing (theory of mind) task, and also in the orbito-frontal cortex (Baron-Cohen et al., 1994). A neuroanatomical study of autism at post-mortem found microscopic pathology (in the form of increased cell density) in the amygdala, in the presence of normal amygdala volume (Bauman & Kemper, 1994; Rapin & Katzman, 1998). Secondly, patients with autism tend to show a similar pattern of deficits to those seen in patients with amygdala lesions (Adolphs, Sears, & Piven, 2001). Thirdly, several structural magnetic resonance imaging studies of autism have revealed abnormal development of the amygdala (see Baron-Cohen, Knickmeyer and Belmonte, 2005 for a

review). A recent, larger structural study suggests more generalized structural abnormalities in the social brain (Critchley, Daly, Bullmore et al., 2000). We have also recently reported a functional dysconnectivity of the amygdala with other brain structures (Welchew et al., 2005).

Ultimately, the cognitive and neural abnormalities in autism spectrum conditions are likely to be due to genetic factors. The sibling risk-rate for autism is approximately 4.5%, or a ten-fold increase over general population rates (Jorde et al., 1991). Regarding twin studies, in an epidemiological study of same-sex autistic twins, it was found that 60% of MZ pairs were concordant for autism vs. no DZ pairs (Bailey et al., 1995). When these authors considered a broader phenotype (of related cognitive or social abnormalities), 92% of MZ pairs were concordant vs. 10% of DZ pairs. The high concordance in MZ twins indicated a high degree of genetic influence, and the risk to a co-MZ-twin can be estimated at over 200 times the general population rate.

Molecular genetic studies are beginning to narrow down candidate regions. There is still little consensus, but two regions have been identified in several (but not all) studies. These are 15q11-13, near the $GABA_A ß_3$ receptor sub-unit gene ($GABRB_3$) and a second one on 17q11.2, near the serotonin transporter gene (SLC6A4). Serotonin innervates the limbic system, and so plausibly plays a role in emotion recognition and empathy. In mice, mothers homozygous for $GABRB_3$ knockout fail to engage in normal nurturing behaviour and have epileptiform EEG (DeLorey et al., 1998; Homanics et al., 1997). At least 4 loci on the X chromosome have also been implicated in autism, and there are of interest for

their power to explain the sex-ratio in autism (markedly biased towards males). These are the neuroligin genes (NLGN3, NLGN4), FMR1 (which causes fragile X syndrome), and MECP2. Several reviews of the genetics of autism literature are available, but this is a fast-changing field (Veenstra-Vanderweele et al., 2004).

As yet, specific genes for autism have not yet been identified, despite the encouraging possibility of candidate regions on chromosomes. The future of research in this field will be not only to isolate the relevant genes but also to understand the networks within which these genes function, and ultimately the relationships between these different causal levels in autism. It is hoped that during this research endeavour there will also be evaluations of the most promising treatments.

5. Clinical implications

Past attempts to teach emotion recognition to adults and children with ASC have either focused on the basic emotions (Hadwin et al., 1996; Howlin et al., 1999) or have been part of social skills training courses, usually run in groups (Barry et al., 2003; Howlin, Baron-Cohen, & Hadwin, 1999; Rydin et al., 1999). These training programs typically do not focus specifically on systematically teaching emotion recognition, but instead address other issues, such as conversation, reducing socially inappropriate behaviour, personal hygiene, etc. In such groups it is difficult to target the individual's specific pace of learning. Finally, such groups are socially demanding and might therefore deter more socially anxious participants.

Other attempts to teach individuals with ASC social skills have used computer-based training (Bernard-Opitz et al., 2001; Bolte et al., 2002; Hetzroni & Tannous, 2004; Rajendran & Mitchell, 2000; Silver & Oakes, 2001; Swettenham, 1996). The use of computer software for individuals with autism spectrum conditions has several advantages: First, individuals with ASC favour the computerized environment since it is predictable, consistent, and free from social demands, which they may find stressful. Second, users can work at their own pace and level of understanding. Third, lessons can be repeated over and over again, until mastery is achieved. Fourth, interest and motivation can be maintained through different and individually selected computerized rewards (Bishop, 2003; Moore et al., 2000; Parsons & Mitchell, 2002). Previous studies have found that the use of computers can help individuals with autism pass false belief tasks (Swettenham, 1996), recognize basic emotions from cartoons and still photographs (Bolte, Feineis-Matthews, Leber et al., 2002; Silver & Oakes, 2001), and solve problems in illustrated social situations (Bernard-Opitz, Sriram, & Nakhoda-Supuan, 2001). However, participants find it hard to generalize their knowledge from learnt material to related tasks.

The computer-based interventions above used drawings or photographs for training, rather than more life-like stimuli. This might have made generalization harder than if more ecologically valid stimuli were used. In addition, the programs teaching emotion-recognition focused on basic emotions, and only on facial expressions. No reported

program to date has systematically trained complex emotion recognition in both visual and auditory channels, with life-like faces and voices.

We have recently evaluated *Mind Reading* (Baron-Cohen et al., 2004), an interactive guide to emotions and mental states, and its value as a tailored teaching tool for emotion recognition for learners on the autistic spectrum. *Mind Reading* is based on a taxonomic system of 412 emotions and mental states, grouped into 24 emotion groups, and 6 developmental levels (from age 4 to adulthood). The emotions and mental states are organized systematically, according to the emotion groups and developmental levels. Each emotion group is introduced and demonstrated by a short video clip giving some clues for later analysis of the emotions in this group. Each emotion is defined and demonstrated in six silent films of faces, six voice recordings, and six written examples of situations that evoke this emotion. The resulting library of emotional 'assets' (video clips, audio clips, or brief stories) comprises 412 x 18 = 7416 units of emotion information to learn to recognize or understand. This is therefore a rich and systematically organized set of educational material. The software was created for the use of children and adults of various levels of functioning. Vocal and animated helpers give instructions on every screen.

We tested for any improvement in *adults* with AS/HFA in emotion recognition skills following *independent* use of the software, and the extent to which these users can generalize their acquired knowledge. The intervention took place over a period of 10-15 weeks, to assure a meaningful period for training, recognizing that a longer duration

might lead to individuals dropping out. Participants were tested before and after the intervention. A no-computer-intervention control group of adults with AS/HFA was matched to the intervention group. This AS/HFA control group was also tested before and after a similar period of time, but had no intervention. The need for a no-intervention AS/HFA group was to assess whether any improvement was related to the intervention or merely due to taking the tasks twice or to time passing. A third, typical, control group from the general population was matched to the intervention groups. This group was only tested once, to obtain baseline measures.

Results showed that following 10-20 hours of using the software over a period of 10-15 weeks, users with ASC significantly improved in their ability to recognize complex emotions and mental states from both faces and voices, compared to their performance before the intervention, relative to the control group. This finding is interesting, considering the short usage time and the large number of emotions included in the software, and since participants were not asked to study these particular emotions (Golan, Baron- Cohen, & Hill, 2006).

The above study illustrates one practical teaching method focused on improving mindreading in ASC, but it should be recognized that other approaches (such as preverbal intervention to encourage the development of shared attention) are also being explored.

6. Future directions

The area of social cognition in ASC remains important, and in this chapter we have necessarily reviewed research in a range of separate areas (cognitive development, neuroimaging, neuroanatomy, genetics, intervention). The hope is that in the future, inter-disciplinary science will take place so that we can integrate these currently disparate areas, and discover which brain regions change as a result of intervention, or are under the control of which genetic mechanisms, in which subgroup on the autistic spectrum.

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