Clinical Research Portfolio Volume I: Appendices

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Systematic Review Figure 1. Flowchart showing exclusion and inclusion selection process

2030 from main search strategy

Plus eight additional papers from hand search, meaning 2038 papers in total

Minus 1830 based on title, leaving 208

Minus 142 based on abstract, leaving 66

Minus 53 based on methodology section, leaving 13

Systematic Review Table 1: Siblings

Study & Quality Rating	Facet of BAP	Measures	Control Group	Age and IQ level of pro-bands	Features of BAP found
Briskman, Happe & Frith (2001), 78%, High	WCC	RSPQ	Siblings of people with dyslexia and of TD children	See original study by same authors below – this study included additional controls and fewer autism and dyslexia participants but new norms not given.	None identified
Dorris, Espie, Knott & Salt (2004), 75%, High	SC	RME-R	TD children matched for gender, age and verbal IQ	Not available	Siblings group showed poorer performance on RME-R ($p = .03$, cohen's $d = .77$; large[2]).
Happe, Briskman and Frith (2001), 78%, High	WCC	EFT, BD, TV, SCT	Two control groups: relatives of children with dyslexia and relatives of TD children	Children with a mean age of 12 years (SD 3 years), Mean IQ 90 (SD 19)	Siblings made fewer errors than TD children on TV ($p = .008$) [1]
Spencer, 2011, 77%, High	Brain function, response to emotion	Computerised implicit facial emotion processing task (CIFEP),	Control group of TD children, not matched for gender, group matched on age and IQ	Children with mean age = 14.56 (SD 1.74), mean IQ = 106.5 (SD 16.6)	Activation in siblings was significantly reduced compared with controls for 7/11 brain regions: the left superior frontal gyrus ($p = 0.001$), the right ($p = 0.002$) and left ($p = 0.005$) temporal poles, the right middle ($p = 0.004$) and left posterior ($p = 0.016$) STS, the left dorso-medial prefrontal cortex ($p = 0.005$) and the right FFA ($p = 0.044$). [1] When watching happy faces, activation in the autism group did not differ from activation in siblings.

Yoder, Stone, Walden & Malesa (2009), 73%, Medium	SC	MSEL, RJA, SBC	Siblings of TD children	Not Available	Initial language level was predictive of eventual ASD diagnosis (p = .04). SBC and RJA scores in siblings at time 5 were significantly below TD group (medium effect size; cohen's d = .673; medium[2]). RJA (p = .04) and WTC (p = .02) predicted the degree of social impairment at the end of the study.

1. Where effect sizes are not given this is due to a lack of appropriate data available for use in calculations.

2. Cohen (1988) defines <.2 as a small effect, .5 as medium and >.8 as a large effect size.

Systematic Review Table 2: Parents

Study & Quality	Facet of BAP	Measures	Control group	Age and IQ level of pro-bands	Features of BAP found
Baron-Cohen & Hammer (1997), 53% Medium	EF and SC	EFT, RME	Parents of TD children matched for age, IQ, SES and educational level	Not Available	Parents quicker on EFT; Fathers vs. control males; ($p = .01$, cohen's $d = -.7$, medium); Mothers vs. control females; ($p < .005$, cohen's $d = -.527$, medium), and less accurate on RME; Fathers vs. control males; ($p = .004$, cohen's $d = -1.019$, large); mothers vs. control females ($p = .0001$, cohen's $d = -1.56$, large)
Baron-Cohen, Ring, Chitnis, Wheelwright, Lloyd, Gregory, Williams, Brammer & Bullmore (2006), 70% Medium	EF and SC	EFT, RME	Neuro-typical adult controls matched for gender, IQ and SES	Not Available	Parents showed less activity in extra-striate cortex during EFT than their matched controls in two brain regions – the right middle occipital gyrus ($p = .002$) and the lingual gyrus ($p = .001$). Parents showed less activity in the left middle temporal gyrus ($p = .001$), and in the left ($p=.007$) and right inferior frontal gyrus ($p=.003$) than their matched controls during the RME. [1]
Briskman, Happe & Frith (2001), 78%, High	WCC	RSPQ	Parents of people with dyslexia and of TD children	These details given for original study by same authors above – this study included additional controls and fewer HFA/AS and dyslexia participants but new norms not given.	Both mothers and fathers of boys with HFA/AS showed social ($p < .05$, cohen's $d = .965$, large) and non-social preferences ($p = .006$, cohen's $d = .803$, large) fitting with WCC.
De Jonge Kemner & van Engeland (2006), 75%,	EF	EFT	Parents of children with Downs	Mean age 18.9 (SD 8 years), Mean IQ 100.3	Fathers of pro-bands made fewer incorrect attempts before finding the correct shape on EFT ($p < .004$, cohen's

High			Syndrome	(SD 17.3)	d = -.563, medium).
Happe, Briskman and Frith (2001), 78%, High	WCC	EFT, BD, TV, SCT	Two control groups: relatives of children with dyslexia and relatives of TD children	Children with a mean age of 12 years (SD 3 years), Mean IQ 90 (SD 19)	Autism fathers performed better than control fathers on unsegmented BD (p = .034). Fathers were also significantly faster on BD (p = .001, cohen's d = -1.01, large). Autism fathers outperformed dyslexia fathers on TV (p = .016). Autism fathers were also significantly faster than dyslexia or control fathers on the EFT (p = .005, cohen's d = 1.11 (large) and 1.09 (large) for control and dyslexia fathers respectively.
Koczat, Rogers, Pennington & Ross (2002), 59%, Medium	EF: Spatial Working Memory	Two Delayed Oculomotor Response Eye Movement Tasks	Neuro-typical adults group-matched for age and gender	Two-three year olds free from associated medical conditions or complications. IQ data not available.	Parents showed poorer spatial accuracy than controls (p = .03, cohen's d = 1.246, large).
Lennox, Callias & Rutter (1977), 60%, Medium	Cognitive Characteristics; Thought Disorder	OST, GTTDr.	Parents of TD boys	Boys aged 6-16 with a non-verbal IQ of 80 or above (means not given)	None
Losh & Piven (2007), 66%, Medium	SC	RME, MPAS-R, PRS,FI	Parents of TD children	Not given – "high functioning varied in age".	Parents classified as aloof (BAP +) performed worse than all other groups; control (p < .005; Cohen's d = 1.51, large), BAP (-) (p < .005; Cohen's d = 1.49, large) and rigid (p < .005; Cohen's d = 1.48, large). Both the PRS and the FI were significantly associated with the Eyes Test Scores (p < .005). Aloof parents committed significantly more pragmatic language errors in conversational interaction than rigid (p < .01, cohen's d = 1.244, large) or BAP (-) parents (p < .05, cohen's d = -.945, large) and

					reported significantly lower quality friendships than both rigid ($p < .05$, cohen's $d = 1.17$, large) and BAP (-) parents ($p < .0005$, cohen's $d = -1.72$, large).
Losh, Adolphs, Poe, Couture, Penn, Baranek & Piven (2009), 71%, Medium	SC, EF	SC Tasks: RME, MFT, TFT, MST, PLT, EF tasks: ToH, TMT, EFT, SCT, BD	Neuro-typical parents	Young Adults Age Mean 21.5 (SD 5.5) IQ Mean 101.2 (SD 18.1)	BAP findings on all tasks in the domain of SC ($p < .05$) for social BAP (+) group, but not on EF tasks; no differences between BAP (-) group and controls. 41% of fathers vs. 16% of mothers showed the social BAP.
Scheeran & Stauder (2008), 64% Medium	SC	AQ, BD, CVDT	Parents with TD children	Children aged 6-16; 9 years five months mean age, SD not given. IQ not measured but recruited through school which only accepted children with IQ > 70.	Fathers whose child had HFA/AS responded slower to social cues than control fathers ($p = .032$, cohen's $d = .93$, large).
Whitehouse, Barry & Bishop (2007), 64%, Medium	Language	AQ, TROG-2, TOWRE; Sight Word Efficiency and Phonemic Decoding Efficiency Sub-tests, WISC-R; Digit Span, NEPSY; Oromotor Sequences and Repetition of nonsense words, speeded dictation	Parents of children with a language impairment, parents of TD children	All male pro-band group. Mean age, 10 years 4 months, SD 2 years 6 months. Mean IQ 109.48, SD 14.58	On subscales of the AQ (communication; $p <.05$, cohen's $d = .65$, medium) and attention switching ($p <.05$, cohen's $d = .68$, medium), parents of children with HFA/AS showed elevated scores in comparison to controls. They showed better language performance than the parents of children with language impairments ($p < .05$).

Full titles of measures cited in tables: Autistic Spectrum Quotient (AQ), Bannister-Fransella Grid Test of Thought Disorder (GTTD) Block Design (BD) Spencer (2011) computerised implicit facial emotion processing task, {Vlamings, 2005) computerised visual detection task, (CVDT) Friendship Interview, FI Goldstein-Scheerer Object Sorting Test (OST) Modified Personality Assessment Schedule-Revised, (MPAS-R); Mullen Scales of Early Learning (MSEL), NEPSY: a developmental neuropsychological assessment), Pragmatic Rating Scale (PRS) Reading the Mind in the Eyes (RME), Real life styles and preference questionnaire (RSPQ) Screening Tool for Autism in Two-Year-Olds, Responding to Joint Attention (RJA), Sentence Completion Task (SCT) Social Behaviour Checklist (SBC) Test for Reception of Grammer-2 (TROG-2), Test of Word Reading Efficiency,

TOWRE The Embedded Figures Test (EFT), The Morphed Faces Task (MFT),The Movie Stills Task (MST), The Point Light Task (PLT), The Tower of Hanoi (ToH), The Trail Making Task (TMT), Titchener Circles Illusion (visual illusions version) (TV), Trustworthiness of Faces Task (TFT), Wechsler Intelligence Scale for Children-Revised (WISC-R).

1. Where effect sizes are not given this is due to a lack of appropriate data available for use in calculations.

2. Cohen (1988) defines <.2 as a small effect, .5 as medium and >.8 as a large effect size.

APPENDIX 1.1 SYSTEMATIC REVIEW: ADAPTED STROBE STATEMENT

— CHECKLIST OF ITEMS CONSIDERED IN DETERMINING STUDY QUALITY

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (score = /1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (score = /1)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (score = /1) Gives a definition of what the authors mean by phenotype, or equivalent term (score = /1)
Objectives	3	State specific objectives, including any pre-specified hypotheses (score = /1)
Methods		
Study design	4	Present key elements of study design early in the paper (score = /1)
Setting	5	Describe the setting (score = /1), locations (score = /1), and relevant dates, including periods of recruitment (score = /1), exposure (score = /1) and data collection (score = /1)
Participants	6	(*a*) *Case-control study*—Give the eligibility criteria (score = /1, if for both cases and controls, 1 point, for one or other, half point), and

		the sources (score /1, half point if just for cases or controls) and methods of case ascertainment (score /1) and control selection (score /1). Give the rationale for the choice of cases and controls (score /1).
		(*b*) *Case-control study*—For matched studies, give matching criteria (score /1) and the number of controls per case (score /1) (*c*) Did the article specify the specific diagnosis for AS/HFA participants (score = /1) and was the method of diagnosis appropriate (e.g. by multidisciplinary team, using an ADOS)? (score = /1) (*d*) Were the characteristics of subjects clearly described (e.g. demographic information such as age (score = /1), gender (score = /1))?
Variables	7	Clearly define all outcomes (score = /1), exposures (score = /1), predictors (score = /1), potential confounders (score = /1), and effect modifiers (score = /1).
Data sources/ measurement	8*	For each variable of interest, give sources of data (score = /1, if for some and not others, gets half a point) and details of methods of assessment (measurement) (score = /1, if for some and not others, gets half a point). Are measures age-appropriate? (score / 1)

Bias	9	Describe any efforts to address potential sources of bias (score - /1)
Study size	10	Explain how the study size was arrived at (score = /1)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. (score = /1)
Statistical methods	12	(*a*) Describe all statistical methods, (score = /1, give half a point if partial description) including those used to control for confounding (score = /1)
		(*b*) Describe any methods used to examine subgroups and interactions (score - /1)
		(*c*) Explain how missing data were addressed (score = /1)
		(*d*) *Case-control study*—If applicable, explain how matching of cases and controls was addressed (score = /1)
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study— numbers potentially eligible (score = /1), examined for eligibility (score = /1), confirmed eligible (score = /1), included in the study (score = /1), and analysed (score = /1)
		(b) Give reasons for non-participation at each stage (score = /1, give half a point if partially gives reasons)
		(c) Use of a flow diagram (score = /1)

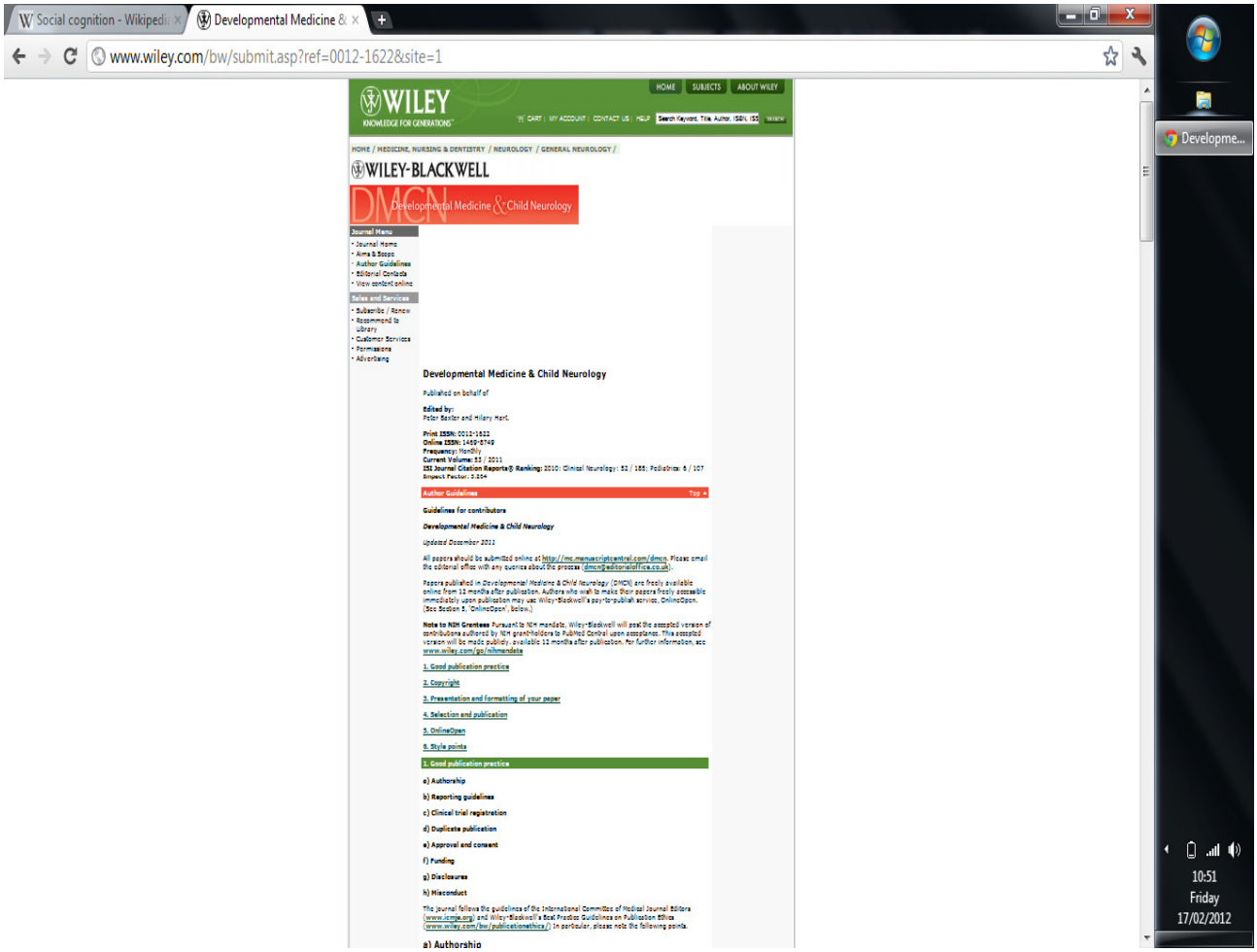
Descriptive data	14*	(a) Give characteristics of study participants (e.g demographic (score = /1), clinical (score = /1), social (score = /1)) and information on exposures (score = /1) and potential confounders (score = /1)
		(b) Indicate number of participants with missing data for each variable of interest score = /1, gets half a point if gives partial information on missing data)
Outcome data	15*	*Case-control study*—Report numbers in each exposure category, or summary measures of exposure (score = /1)
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g, 95% confidence interval) (score = /1, gets half a point if offers either or). Make clear which confounders were adjusted for (score = /1) and why they were included (score = /1)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions score = /1
Discussion		
Key results	18	Summarise key results with reference to study objectives (score = /1)
Limitations	19	Discuss limitations of the study, (score = /1) taking into account sources of

		potential bias or imprecision (score = /1). Discuss both direction (score = /1) and magnitude (score = /1) of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, (score = /1) limitations (score = /1), multiplicity of analyses (score = /1), results from similar studies (score = /1), and other relevant evidence (score = /1)
Generalisability	21	Discuss the generalisability (external validity) of the study results (score = /1)
Other information		
Funding	22	Give the source of funding (score = /1) and the role of the funders (score = /1) for the present study Final score = /69

*Should give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 1.2 DMCN Author Guidelines



Major Research Project Table 1: Descriptive statistics for groups and subgroups on the dependent variables

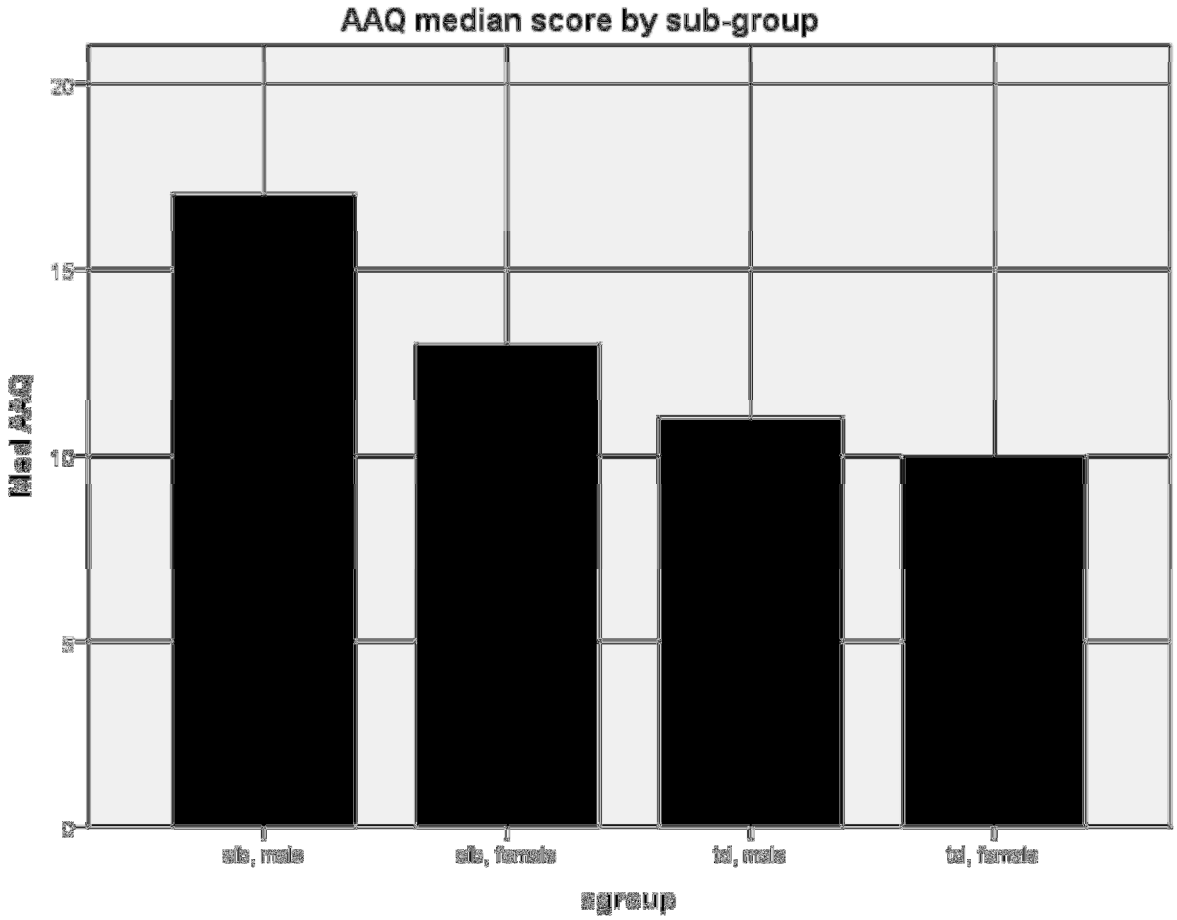
DEPENDENT VARIABLE	MEAN (SD)	MEDIAN (RANGE)
AAQ*		
Whole Sample	13.3 (9.3)	11 (3-44)
Sibling group	14.8 (10.9)	14.5 (3-44)
Control group	11.8 (7.6)	10.5 (3-27)
Male Siblings	20.4 (14.9)	17 (3-44)
Female siblings	10.9 (5.1)	13 (4-17)
Male Controls	12.2 (9.3)	11 (3-27)
Female Controls	11.5 (7.5)	10 (4-26)
RME Total Score		
Whole Sample	20.1 (2)	20 (15-24)
Sibling group	19.8 (2.3)	20 (15-23)
Control group	20.4 (1.8)	20 (18-24)
Male siblings	19.8 (1.7)	20 (17-22)
Female siblings	19.9 (2.8)	20 (15-23)
Male controls	20.6 (2.2)	20 (18-24)
Female controls	20.3 (1.8)	20 (18-23)
RME Mean Time*		
Whole Sample	146.8 (310.8)	55.5 (2-1603)
Sibling group	230.6 (425.5)	107 (2-1603)
Control group	63 (70)	53 (7-280)
Male siblings	366.5 (615.9)	128 (2-1603)
Female siblings	114.1 (108.6)	107 (23-345)
Male controls	81.8 (112.9)	52 (7-280)

Female controls	44.6 (20.1)	53 (9-64)
RMV Total Score		
Whole Sample	15.1 (3)	15 (10-20)
Sibling group	15.3 (2.9)	15 (11-20)
Control group	14.9 (3.1)	16 (10-20)
Male siblings	15.8 (3.2)	16 (12-19)
Female siblings	14.9 (2.8)	15 (11-20)
Male controls	15.7 (3.4)	15.5 (11-20)
Female controls	14.3 (3)	16 (10-18)

*As AAQ and RME mean response time data were drawn from a small sample and appeared not to be normally distributed, it may be that the median and range represent a more informative depiction of the data than the mean and standard deviation.

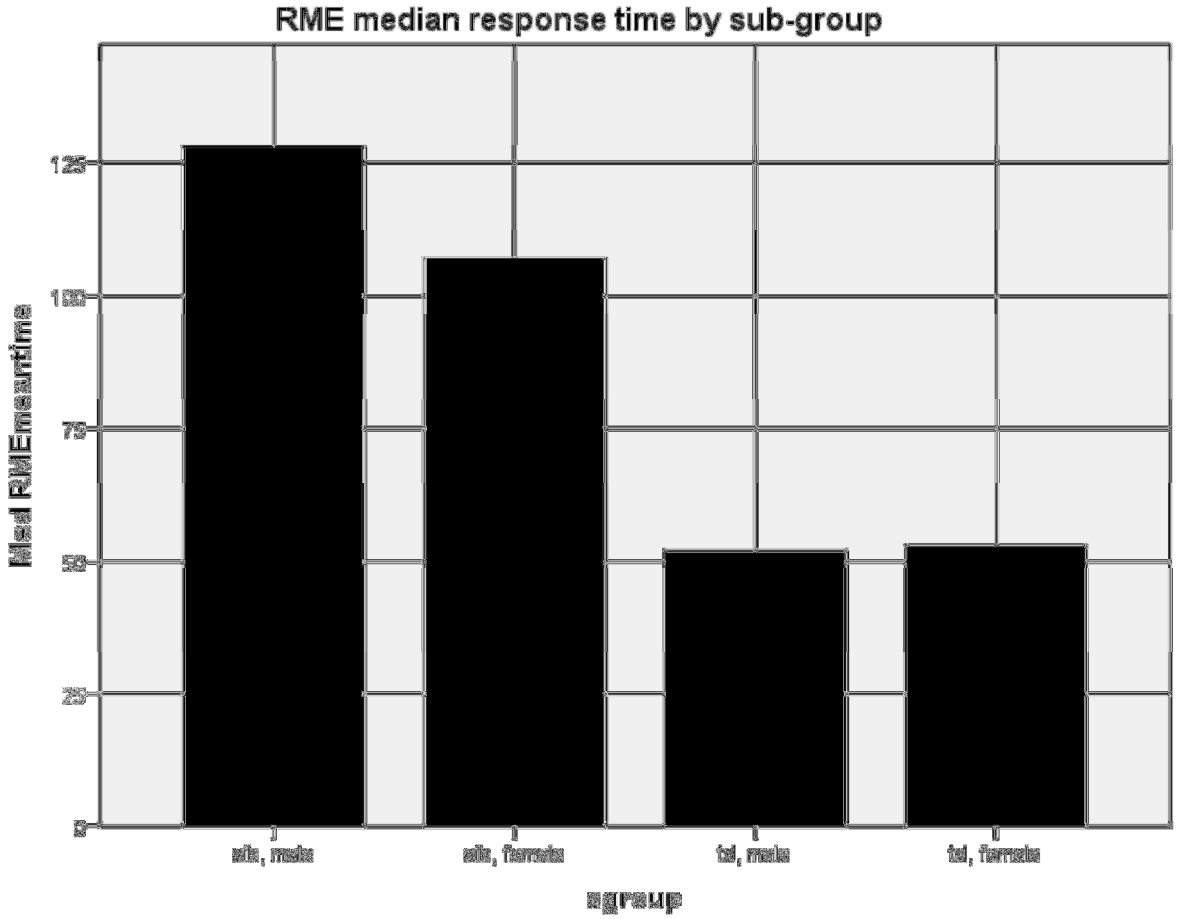
Major Research Project Figure 1: Median AAQ scores by sub-group

Visual inspection suggests that the male siblings appear to have the highest mean AAQ score of any sub-group, with female siblings having a slightly higher median number of traits than girls without a relative on the autistic spectrum.

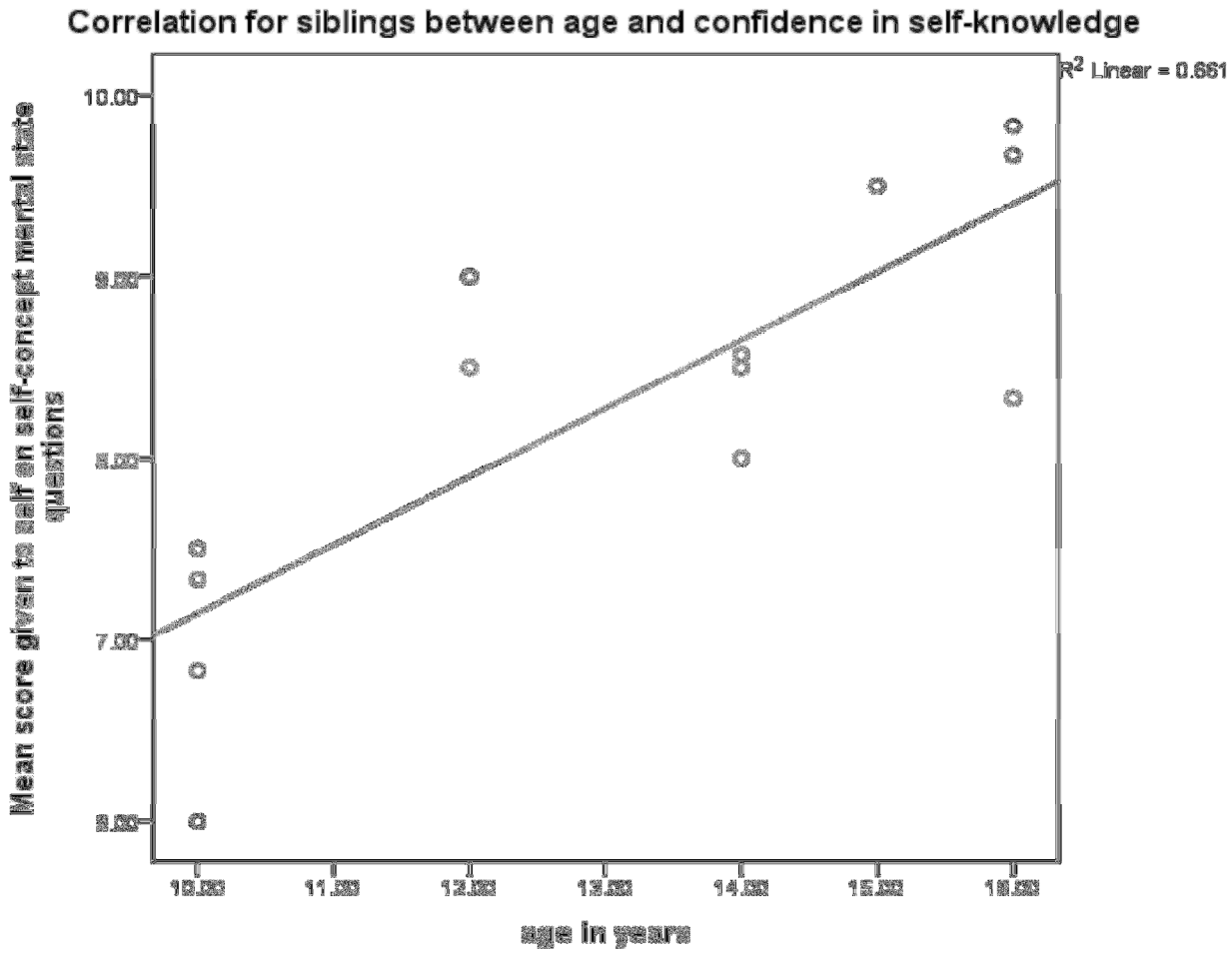


Major Research Project Figure 2: Median response time on RME by sub group

Visual inspection suggests male siblings had the longest response times.



Major Research Project Figure 3: Confidence in self-knowledge increases with age for the sibling group



Appendix 2.1: JCPP Author Guidelines

APPENDIX 2.2 MAJOR RESEARCH PROPOSAL: MENTALISING ON THE BROADER AUTISM PHENOTYPE: A GLOBAL OR MODULAR IMPAIRMENT?

People with Asperger's Syndrome/ High Functioning Autism (AS/HFA) have difficulty across a triad of impairment comprising social interaction, communication and imagination. A recent prevalence estimate found 157 people with Autism Spectrum Conditions (ASCs) per 10,000 of the population (1). A number of cognitive theories of autism have been influential, one hypothesis being that social communication difficulties stem from impaired theory of mind (ToM) (2). Previous studies have established that children with AS/HFA have particular difficulty with understanding both others' minds (3) and their own (4).

There is considerable evidence for a genetic basis of AS/HFA, with the implication that relatives are likely to share these autistic traits to a greater or lesser extent (5, 6). In identical twin pairs, one member of whom has autism, the concordance rate for autism is 60% and the concordance rate for a disorder on the autism spectrum is over 90% (7). Another study found that about half of all boys diagnosed with AS/HFA have a paternal family history, and 71/100 individuals with AS/HFA had one or more first or second-degree relatives who had raised some suspicion of suffering from the disorder (8). However, the search for unequivocal evidence of autism susceptibility genes continues, due to analytical and methodological challenges. Limited power, varying designs, genotyping and analyses and imprecise phenotypic definitions are some of the limitations (6). A Broad Autism Phenotype (BAP) has been shown to characterize relatives of people with AS/HFA (5, 7-10). BAP mild impairments identified in relatives include those in the domains of language, social functioning, restricted interests and behaviour and neurocognitive functioning (6). If this is the case, support for the whole family may be the most appropriate intervention, and greater importance may be attached to prospective examination of the development of AS/HFA where one sibling is known to be affected (7). Particularly, consideration should be given to the communication style and needs of family members in supporting the child with autism.

Considerable interest has therefore been devoted in the research literature to examining the cognitive phenotype of AS/HFA in first-degree relatives, including siblings. Several studies have shown that siblings also have difficulties with ToM tasks, such as "Reading the Mind in the Eyes (RME-R)" (9). However, perhaps due to methodological differences and weaknesses other studies have not detected significant differences between siblings and typically developing (TD) children (10), posing questions as to the sensitivity of tests in detecting the more subtle impairment likely in those affected by the BAP. Studies have not generally recorded response time for siblings, which may indicate level of effort or 'cognitive fluency' in completing the task. One study found that while children with AS/HFA were globally slower to respond on a range of cognitive tasks than controls, they were particularly slow on a mental state inference task (2). It may be that while siblings can correctly decipher emotions, it might be more challenging and so take them longer to do so. In naturalistic social situations, this could lead to subtle impairment. It may also be that the degree of autistic traits determines performance on ToM measures, rather than simply whether or not one has a sibling with AS/HFA. This suggestion was evidenced by another study (12), which found that the more autistic traits their adult participants had, the lower their scores on the RME-R and the Reading the Mind in the Voice test – Revised (RMV-R).

Another question arises as to whether ToM deficits are specific to a particular sensory modality or are multi-modal. The RMV-R (Adult) has been positively correlated with the RME-R (Adult) in neurotypical adults, suggesting a common basis for emotion and mental state recognition abilities across perceptual domains (13), however as limited evidence has been provided more research is needed to clarify this.

While ToM difficulties among AS/HFA populations are well established, recent research has examined self-mentalising ability. Difficulties such as in accessing, representing and expressing thoughts and feelings may seriously impact social competence and hold strong associations with communicative barriers evident in autism (14). TD children attribute more knowledge about their

own internal states to significant others until around the age of 10 (15). It has been demonstrated that children as young as six recognize that aspects of self-knowledge that can be discerned through external cues are easier for other people to identify than aspects that are primarily manifested internally (15). Researchers have also investigated attributions about expertise in knowledge (16) and found a gradual shift from parents to friends, siblings and self being judged the experts. This shift commenced at around age 9 and was completed by early adolescence. In a study of self-concept (4) a measure of self-concept was administered to a group of young adolescents with HFA/AS and a group of TD control children. The measure included two control questions to check the children understood the task and six focal self-knowledge questions. These questions required the young person to reflect on whether they or an identified other knew more about their own internal states. Those with AS/HFA thought others knew more than them about their own internal states, whereas TD matched controls stated clearly that they had superior knowledge about their own internal processes, suggesting a diversion from typical adolescent development in self-mentalising in AS/HFA.

It is currently debated within the literature whether self-mentalizing may be a pre-requisite for understanding others' minds, or whether it develops once the concept of ToM is established. A meta-analysis found no evidence of self/other asymmetry in development (17). Some evidence indicates children with autism had difficulty identifying their own intentions in comparison to TD children (17). It has been suggested that while self and other mentalising may both be impaired in AS/HFA, the impairment may differ in magnitude (17). Siblings, in addition to experiencing subtle deficits in ToM, may also show less understanding of their own minds. If so, this would add to our understanding of the mechanisms underpinning ToM processes within the BAP.

The AAQ (18) is a measure of severity of autistic traits and can allow exploration of variance in performance on tasks known to be impaired in HFA/AS which is explained by scores on a general measure of BAP. This then enables the question of whether there is a global deficit on the BAP in

mentalising about both self and others, which can be detected by scores on a general measure. Alternatively, a pattern of modular strengths and weaknesses may prevail which could not be predicted solely by AQ score. An argument has been presented to support this (14), hypothesizing that distinct impairments may segregate independently as distinct endophenotypes on the BAP. Behavioural features of the BAP were examined in relation to performance on the RME-R with parents of children with autism (14). Parents were not found to be impaired in general, but those classified as aloof during a personality interview displayed significant social cognitive deficits on the RME-R. Poorer performance was in turn associated with poorer quality friendships and problems with pragmatic language use. Identifying such endophenotypes may provide a way to isolate specific neuropsychological mechanisms of biological and genetic significance to autism. This goal is of interest conceptually, in terms of the breadth of impairment on the BAP and the proposed theoretical link between the ability to mentalise about self and about others (17).

In recent years, there has been debate in the literature as to whether there are significant differences between children diagnosed with Asperger's Syndrome versus with High Functioning Autism. One study (19) examined this and found no differences on language ability, Autism Diagnostic Interview-Revised (ADI-R) scores or social outcome. For the present study, no distinctions will be made.

Aims

To explore the question of whether deficits in mentalising are global on the BAP, or whether it is possible to have a pattern of preserved skills in some areas and weaknesses in others. Following on from this, to investigate whether scores on a general measure of BAP can predict performance on mentalising tasks.

To investigate the possibility that siblings may have more autistic traits than TD peers and that this may impact upon their ToM and self-concept capabilities.

We also aim to explore the relative effort or 'fluency' demonstrated by siblings in relation to controls when solving these mentalising tasks, and whether performance on auditory and visual modalities correlate in support of a shared underlying ToM module.

Research Questions

1. Do siblings have more autistic traits than TD peers?

2. Is there a relationship between overall AQ score and performance on the target measures?

3. Is it more effortful for siblings to solve mentalising tasks than for TD children?

4. Are siblings impaired in ToM tasks across sensory modalities?

5. Do siblings have a general impairment in self-mentalising?

Hypotheses

It is hypothesised that siblings may be subtly impaired on ToM tasks in terms of both test performance and response latency; and that these difficulties will be apparent across sensory modalities. It is further hypothesized that siblings will additionally be impaired on self-concept tasks. It is hypothesized that AAQ score will explain variance in scores on the RME and the RMV, and perhaps the self-concept task.

Plan of Investigation

Participants

Two groups of participants will be required: siblings of children with a diagnosis of AS/HFA and a control group matched for gender, as it is thought that autism may affect females and males differently and that TD girls may outperform boys on the target measures (9, 18). As both verbal IQ and age have been shown to affect performance on ToM measures, participants will be matched as closely as possible for these variables (20).

Inclusion and Exclusion Criteria

Participants will be at least ten years of age given that current literature suggests understanding of privileged access to one's own mental states only emerges at this point for TD children. Inclusion criteria for the siblings group would include a sibling diagnosed with AS/HFA. Exclusion criteria for the TD children would include having special educational needs or a score on the AQ over 30, as it may be that there are children in the general population with a diagnosis who have not come to the attention of health or educational professionals (1), and such variance, while to be expected, would confound our results (18). Appropriate preparations will be made in the event that any young people or their parents had concern regarding their social communication following participation in the study (see ethics).

Recruitment Procedures

Siblings of children with HFA/AS will be recruited from the Scottish Centre for Autism, and also from the Community Autism Teams across the four Community Health Partnership areas in Greater Glasgow. Presentations will be given to facilitate recruitment through these clinical teams following ethical approval to raise awareness of the study, its purpose and theoretical aims. Clinicians in neighbouring health boards have also been approached to establish whether they could act as an additional point of contact for recruitment should higher numbers be required. Additional participants may also be sought from support groups affiliated with the National Autistic Society across Scotland. TD children will be sought by writing to local schools following ethical approval from the relevant Education Authority.

Measures

<u>Adolescent Autism Spectrum Quotient (AAQ) (18)</u>

This is a parent-report questionnaire, adapted from the Adult AQ, which measures the degree to which any child aged 9-15 possesses traits related to the autism spectrum. In itself it is not however

a diagnostic measure. Scores range from 0 – 50, with higher scores reflecting more traits. Using a cut-off score of 30, no controls scored above this level but all AS/HFA girls and 86.7% of the AS/HFA boys did. It also showed good test-re-test reliability and high internal consistency.

The British Picture Vocabulary Scale (BPVS, 21).

The BPVS is a picture-based measure of receptive vocabulary, standardized for children aged 3 to 18. While the measure has a fairly low ceiling, which can be problematic for able adolescents with a good vocabulary (19), as the target population are younger adolescents this should not prove too much of an issue. Additionally, the measure has the advantage of taking only five minutes to administer, thus conserving testing time.

Self-concept Questionnaire (22)

This measure requires participants to first identify a comparison individual. Each participant then participates in a verbally administered self-concept interview in which they are asked to rate first their own expertise and then the comparison individual's expertise on two control questions and six focal self-knowledge topics including knowing when you feel ill, tired, sad, happy, are daydreaming and about what kind of person you are (see appendix 2.4).

Child Reading the Mind in the Eyes test (RME) (3)

This task is a modified version of the original adult version of the RME-R task. The main adaptation is reduced complexity in vocabulary. It is a computer based task, supported by verbal explanation from the experimenter. It has 28 items, in which participants are presented with a photograph of the eye area of the face and are asked to choose from four adjectives to describe the person's mental state. These items include subtle emotions, and a practice item precedes the first trial. Lesion and fMRI studies have implicated specific neural circuitry involved with performance on the RME, suggesting that this measure may be particularly well suited to investigating biological pathways for studies of the brain and the genetic basis of autism (14).

Reading the Mind in the Voice test (RMV) (12)

This measure has been shown to have good reliability and discriminative validity. Again, this is a computer based task, with the child required in this instance to decide from a choice of four adjectives which best represents the mental state of the speaker of a voice clip. Unfortunately this measure has not been modified as yet for younger children: however, as adolescents are the target group in this study this should not prove problematic. Definitions of words are provided on a handout, which children can familiarize themselves with prior to participating in the task, reducing any issues regarding impact of vocabulary. Where necessary the experimenter can supplement this with further explanation of word meanings prior to task commencement.

Design

The study will employ a matched samples design. The independent variable is group. The dependent variables will be score on RME test, latency on RME test, Score on RMV test, latency on RMV test, Score on self-concept measure and AAQ score. Control variables include BPVS score, age and gender.

Research Procedures

Diagnosis of index children will be ascertained prior to participation in the study by parent completion of a brief questionnaire (see appendix 2.3), followed by contacting the team who made the diagnosis or viewing confirmatory paperwork. Parents of both groups of children will also be asked to complete the AAQ. AAQ scores can be used to measure whether siblings generally have a higher number of autistic traits than randomly selected TD children. Additionally, AAQ scores can reveal whether autistic traits predict performance on target measures. The BPVS will be used to measure and control for verbal IQ, as some previous studies suggest this may have a bearing on performance on ToM tasks (10). All children will additionally complete the RME, the RMV and the Self Concept questionnaire. Latency data for the ToM tasks will be recorded using a stopwatch,

following a tight protocol (2), although DMDX software will automatically record this. As soon as the test question is asked, the stopwatch will start. When the participant answers, the stopwatch will be stopped and the exact answer recorded. Effort will be made to time discreetly so as not to cause undue anxiety. Testing time is likely to be approximately 1 hour, but this would be established by a pilot study. The RMV and RME take 20 minutes each to administer respectively (12); the BPVS takes five minutes (4) and the self-concept questionnaire around ten minutes (4).

Justification of Sample Size

A power equation, calculated using PASS 2008 software and following the procedure indicated by Mueller (23,24), was utilized to establish the number of participants required for Multivariate Analysis of Variance (MANOVA). Using data from previous studies which used the target measures (3, 4, 12); a means matrix and covariance matrix were produced. Due to large effect sizes produced in studies using the target measures, the power calculation indicated that if a Wilks Lambda approximate F test was used a sample of 25 participants per group would be adequate to test the hypothesis with .8 power at $p < .05$. Therefore, 25 siblings of children with AS/HFA and 25 siblings of TD children will be asked to participate.

Settings and Equipment

Participants will largely be seen in either a clinic setting or their own school. Equipment will comprise a laptop with the computer based tasks installed, which are run using DMDX software. The DMDX software will record correct responses and latency data in Microsoft Excel.

Data Analysis

Descriptive statistics will be used to examine sample characteristics. Presuming data are parametric, inferential statistical analysis is likely to involve an initial related samples t-test to clarify there are no significant differences in verbal IQ or age between the groups. Presuming no significant differences are found MANOVA will be computed to reveal main effects. Significant interactions could then be investigated with post-hoc related samples t-tests to examine differences between groups on target measures and latency scores.

Research Questions

Do siblings have more autistic traits than TD peers?

A post-hoc related samples t-test could be used to ascertain if there is a significant difference between groups on mean AAQ score.

Is there a relationship between AAQ score and performance on the target measures?

MANOVA could be used to answer this question.

Is it more effortful for siblings to solve ToM tasks than for TD children?

A related samples t-test could clarify if there is a significant difference in mean latency between the groups.

Are siblings impaired in ToM tasks across sensory modalities?

MANOVA main effects could address this question – for example, if there is a main effect for group and RME but not group and RMV score, that would indicate a difference across modalities.

In addition to previously documented impairment in mindreading (others) are siblings also impaired in self-mentalizing?

Previous analyses (4) to examine differences between groups on the self-concept measure could be replicated. A 2 group (HFA/AS vs. TDA) by 2 (self vs. comparison other) by 2 (question topic: programme I like versus the programme my comparison person likes) ANOVA would clarify whether groups differed on control questions. A 2 (group: HFA/AS versus TDA) by 2 (rating: self vs. comparison individual) by 6 (question) ANOVA would subsequently be conducted on participants' ratings on focal questions. Should a 3-way interaction emerge, the groups would be examined separately regarding the interaction between question and rating using a 2 (rating) x 6 (question) ANOVA. Bonferroni pair wise comparisons could then be used to explore any main effects.

Timescale

Ideally ethical approval will be obtained during summer 2010 so that schools can be approached in the winter term. Recruitment of siblings would ideally commence around the same time to allow as lengthy a period as possible for data collection. Data collection would preferably be complete by May 2011 to allow for time to analyse results and write up the study.

Ethical issues

<u>Ethical Issues regarding children and measures to tackle these</u>

Care would be taken to ensure that all participants are aware of their right to withdraw at any time and participants' wellbeing will be carefully monitored throughout. In the unlikely event that a child becomes distressed testing will cease immediately and children would be reassured about their performance and not pressed to continue. Their teacher or parent will be informed. As with research involving children in general, child protection guidance will be adhered to as appropriate.

<u>Arrangements to protect confidentiality of participants' information</u>

A computer database of results will be maintained by the researcher. Participants' questionnaires will be kept in a locked filing cabinet. Collected data will be number coded, with participants'

personal details stored separately. Thus at no time will individuals be identifiable on the basis of data collected.

Adolescent AQ (AAQ)

One issue pertains to the use of the AAQ. It is possible that some participants may in fact be undiagnosed children with autistic spectrum conditions themselves. It is possible therefore that AAQ scores could indicate the presence of autistic spectrum traits not otherwise known of. However, the AAQ measures personality traits present on a continuum in the general population, and it is known that many adults who score above threshold on the AQ do not experience any difficulties in daily life (25). A high score on the measure does not therefore necessarily indicate cause for concern, nor is the measure diagnostic in itself (18). In order to develop an appropriate protocol to take account of the ethical issues this poses, the authors were contacted to enquire how they dealt with this issue. Dr Allison advised that this particular ethical issue had never come up in their studies using the AQ, but that it had with other studies using screening instruments in the general population. Onward referral had been required for children scoring above clinical threshold. Dr Allison also cautioned that false positives may arise from high AQ scores. In the event of any child scoring above threshold on the AQ, and they or their parents expressing concern, they could be offered the opportunity to speak with the second author, a Consultant Paediatric Neuropsychologist at RHSC, Glasgow. If it was felt to be merited, they could then seek further assessment via their General Practitioner.

Planned Submissions

Research and Development Department approval will be sought. Ethical approval will be sought from the local NHS Research Ethics Committee via the Integrated Research Application System (IRAS). The Director of Education will be written to in order to obtain permission to approach schools. Following this, approval would be sought from Head Teachers. Parents would then be asked for informed written consent, as would the children themselves. Teachers, parents and children

would be given the opportunity to ask for more information if they wished and given contact details of the researcher so that they could ask more after completion of the study if necessary.

Clinical implications of research proposal

There are key theory-practice link implications, such as whether global deficits in mentalising should be considered synonymous with HFA/AS, or whether strengths and weaknesses vary with severity or cluster and as such should be individually assessed. If siblings score higher on a measure of BAP than TD matched peers this suggests that systemic intervention for families may be appropriate. For example, including siblings in social skills groups may be considered in light of increasing evidence of siblings being affected by BAP. Further evidence to substantiate the link between self-concept and ToM would add to the theoretical base for suggesting that social communication skills interventions may be beneficial, particularly where these comprise an element of self-reflection and self-awareness. Should deficits be particularly evident in one sensory modality, this may lead to targeting the modality in which interventions are delivered to improve effectiveness.

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APPENDIX 2.3: FAMILY INFORMATION QUESTIONNAIRE

Family Information Questionnaire

1. How many children are in your family in total?

2. Have any children in your family been diagnosed with an autism spectrum condition? (If none, you do not need to answer questions 3-7)

3. If yes, how many children?

4. Does anyone else in the extended family have a diagnosis of an autism spectrum condition?

5. What is their diagnosis? If more than one relative, note which relative has which diagnosis.

6. Where was the diagnosis obtained?

7. Which professional gave the diagnosis? (e.g. psychiatrist, paediatrician, clinical psychologist?)

Appendix 2.4: Self Concept Questionnaire

In this task please give ratings on a scale on 0-10 for the questions you are asked. 0 represents a low response and 10 represents a high response. Some of the questions will relate to yourself and some will relate to the person you described as being closest to you or being most helpful you in your daily life.

1. Can you give the name of a programme you like watching on television?

Out of 10, how much do you know about this programme?

Out of 10, how much does <comparison individual> know about this programme?

Can you give any reasons why you gave a higher score for one that the other or why you gave an equal score?

2. Can you give the name of a programme that <comparison individual> likes watching on television?

Out of 10, how much does <comparison individual> know about this programme?

Out of 10, how much do you know about this programme?

Can you give any reasons why you gave a higher score for one than for the other or why you gave an equal score?

3. Sometimes you may feel poorly or unwell. For example, you may have a headache or feel sick.

Out of 10, how well do you know when you feel ill?

When <comparison individual> is with you at the time, out of 10, how well does he/she know when you are feeling ill?

Can you give reasons why you gave a higher score for one than for the other or why you gave an equal score?

4. Sometimes you may feel tired. For example, when it is late at night or you have been working hard.

Out of 10, how well do you know when you feel tired?

When <comparison individual> is with you at the time, out of 10, how well does he/she when you are feeling tired?

How does <comparison individual> know when you feel tired?

Can you give any reasons why you gave a higher score for one than for the other or why you gave an equal score?

5. Sometimes you may feel sad. For example, someone may have upset you or an event has made you feel unhappy.

Out of 10, how well do you know when you feel sad?

When <comparison individual> is with you at the time, out of 10, how well does he/she know when you are feeling sad?

How does <comparison individual> know when you feel sad?

Can you give any reasons why you gave a higher score for one than for the other or why you gave an equal score?

6. Sometimes we may be asked what kind of person we are. We may answer, for example, that we are a friendly person, a kid person or a happy person.

Out of 10, how well do you know what kind of person you are?

When <comparison individual> is with you at the time, out of 10, how well does he/she know what kind of person you are?

How does <comparison individual> know what kind of person you are?

Can you give any reasons why you gave a higher score for one than for the other or why you gave an equal sore?

7. Sometimes you may daydream or think about things. For example, about things you would like to do or places you would want to go.

Out of 10, how well do you know when you are daydreaming?

When <comparison individual> is with you at the time, out of 10, how well does he/she know when you are daydreaming?

Can you give any reasons why you gave a higher score for one than for the other or why you gave an equal score?

8. Sometimes you may feel happy. For example, when you are doing something you enjoy.

Out of 10, how well do you know when you feel happy?

When <comparison individual> is with you at the time, out of 10, how well does he/she know when you are feeling happy?

How does <comparison individual> know when you are happy?

Can you give any reasons why you gave a higher score for one than the other or why you gave an equal score?