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Neuro- and Social-Cognitive Clustering Highlights Distinct Profiles in Adults with Anorexia Nervosa

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ABSTRACT

Objective: This study aimed to explore the neuro- and social-cognitive profile of a consecutive series of adult outpatients with anorexia nervosa (AN) when compared with widely available age and gender matched historical control data. The relationship between performance profiles, clinical characteristics, service utilization, and treatment adherence was also investigated.

Method: Consecutively recruited outpatients with a broad diagnosis of AN (restricting subtype AN-R: $n = 44$, binge-purge subtype AN-BP: $n = 33$ or Eating Disorder Not Otherwise Specified-AN subtype EDNOS-AN: $n = 23$) completed a comprehensive set of neurocognitive (set-shifting, central coherence) and social-cognitive measures (Emotional Theory of Mind). Data were subjected to hierarchical cluster analysis and a discriminant function analysis.

Results: Three separate, meaningful clusters emerged. Cluster 1 ($n = 45$) showed overall average to high average neuro- and social- cognitive performance, Cluster 2 ($n = 38$) showed mixed per-formance characterized by distinct strengths and weaknesses, and Cluster 3 ($n = 17$) showed poor overall performance (Autism Spectrum disorder (ASD) like cluster). The three clusters did not differ in terms of eating disorder symptoms, comorbid features or service utilization and treatment adherence. A discriminant function analysis confirmed that the clusters were best characterized by performance in perseveration and set-shifting measures.

Discussion: The findings suggest that considerable neuro- and social-cognitive heterogeneity exists in patients with AN, with a subset showing ASD-like features. The value of this method of profiling in predicting longer term patient outcomes and in guiding development of etiologically targeted treatments remains to be seen. © 2014 Wiley Periodicals, Inc.

Keywords: anorexia nervosa; neuro-psychology; social cognition; eating disorder

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Introduction

Anorexia Nervosa (AN) is a disabling mental disorder, with reduced quality of life and high levels of co-morbidity.[1] Growing interest in the neurobiological[2–5] underpinnings of eating disorders (ED) has led to the search for neuro- and social-cognitive biomarkers and endophenotypes. Such markers might, individually or combined, contribute to the development of an etiologically based classification of ED, have the potential to inform predictions of treatment outcome and prognosis, and guide development of targeted brain-directed treatments tailored to the particular profile of an individual.[6–8]

Promising neurocognitive markers of AN include set-shifting difficulties, i.e. difficulties switching between different tasks or task demands[9,10] and poor central coherence, i.e. a preference for local (detail-focused) over global ("bigger picture") processing.[11] These neuropsychological weaknesses have been found in discordant sister pairs[12] and persist after recovery, albeit in muted form.[13] However, these difficulties are less pronounced in adolescents[14] than in adult samples and are greater in in-patients compared with outpatients with AN,

suggesting that both stage of illness and severity affect neurocognitive performance.

In addition, research has demonstrated a link between AN and difficulties in Theory of Mind (ToM) and other aspects of socio-emotional processing.[15] ToM is the ability to identify the mental states (thoughts, feelings, beliefs and intentions) of others. Deficits in cognitive and emotional Theory of Mind (eToM) have been consistently found in AN, both in the ill state and after recovery, albeit to a lesser extent.[16,17]

In combination, the neuropsychological features found in individuals with AN, (i.e., poor set-shifting, poor central coherence and poor ToM) resemble those of people with Autism Spectrum Disorders (ASD)[18] and there has been much interest in this overlap (for review see Ref. 19). However, there is some question as to what proportion of AN sufferers show this neuropsychological profile and to what degree. Further to this, the question as to whether these impairments typically occur together (as in ASD) or independently, in other words whether there are specific subsets of patients with distinct neuropsychological profiles remains unclear. Finally there is also the question as to how these neuropsychological features relate to patients' clinical characteristics and service use. Several studies have attempted to answer some of these questions.

One study examined set-shifting abilities using a range of tasks, including the Wisconsin Card Sorting Task (WCST) and the Brixton spatial anticipation task (BSAT) in a large sample of people with a current or past ED, their unaffected sisters and healthy controls.[20] On a composite measure of poor, average and superior set-shifting abilities, 9% of healthy controls, 10% of unaffected sisters, 18% of people recovered from AN, 23% of those with restricting AN, 38% of BN and 46% of binge-purge AN had poor set-shifting. ED participants with poor set-shifting abilities had a significantly longer illness duration, higher levels of ED rituals, and higher levels of psychiatric co-morbidity.

A further study[21] assessed the cognitive and social-emotional functioning of 100 people with a current ED (AN and BN) compared with healthy controls (HCs; $n = 90$) and those recovered from an ED ($n = 35$) using a battery of set-shifting, central coherence, and social-emotional measures. A principal components analysis identified three components: a fragmented perseverative cognitive style, i.e. detail focus, global integration difficulties and rigidity, for which the ED group scored highly, a global flexible cognitive style, for which HCs scored highly, and a socio-emotional difficulties profile, for which those with EDs scored highly. Eleven per-cent of ED participants had extreme scores on all three components and this group had a more severe and chronic form of illness.

Further attempts at neuropsychological profiling in AN, come from a multi-center collaboration, using a comprehensive battery of neuropsychological tasks in adolescents and adults with AN. Preliminary findings from this collaboration suggest that there may be a range of different neuropsychological profiles in AN samples[22] and also that there may be a distinct pattern of strengths and weaknesses within AN when compared with a normal population.[23]

In addition, a recent pilot study investigated treatment adherence in adult inpatients with AN who were divided into those with high or low ASD traits. A larger proportion of patients with high ASD traits completed treatment as planned compared with those with low ASD traits (high-ASD 87.5%, low-ASD 50%), although this effect did not reach statistical significance.[24]

The main aim of this study is to explore the neuro- and social-cognitive profile in a consecutively recruited series of adult out-patients with AN, with a broad range of illness severity and chronicity. Performance is measured using a small battery of widely used neurocognitive tasks, compared with age and gender matched historical control groups and subjected to cluster analysis. The secondary aims are to investigate whether cluster-group membership is explained through the demographic and clinical characteristics of the sample and to examine relationships with past service utilization and current treatment adherence.

Cluster analytic methods have been widely used in the psychosis field to characterize cognitive heterogeneity. This work has suggested that meaningful replicable clusters emerge with associated differences in clinical symptoms, community functioning, treatment response and outcomes.[25–27]

Analogously, we hypothesize that there will be an ASD-like cluster showing both neuro- and social-cognitive impairment, and that this cluster will have a more severe and chronic form of the illness, together with greater past service utilization and better current treatment adherence.

Method

Participants

Consecutively referred female adult outpatients who fulfilled DSM-IV diagnostic criteria for AN or Eating Disorder Not Otherwise Specified AN-Subtype (EDNOS–AN) and who had a BMI below 18.5 kg/m^2 were included.

Participants were recruited from four UK eating disorder services: South London and Maudsley NHS Foundation Trust; North East London Foundation Trust Eating Disorders Service; Barnet, Enfield & Haringey Mental Health NHS Trust and Oxford Health NHS Foundation Trust. DSM-IV diagnoses were made by senior ED clinicians at patients' initial clinical assessment. Exclusion criteria were poor literacy, non-fluent English, pregnancy or current severe co-morbidity precluding assessment or requiring treatment in its own right (e.g., acute suicidality, substance dependence, psychosis).

All participants were given an explanation of the study and the opportunity to ask questions. They then provided written informed consent to participation. Ethical approval was granted by the Joint South London and Maudsley NHS Trust Research Ethics Committee.

Participants completed the neuro- and social-cognitive battery as part of their baseline assessment for a randomized controlled trial (RCT) comparing two psychological treatments for AN.[28] Participants who did not complete the full testing battery ($n = 26$), had an age ($n = 8$) or IQ score ($n = 8$) ±2 standard deviations from the sample mean were removed from the dataset. This resulted in a final sample $n = 100$. The mean IQ for included participants, as measured by the NART, was 107.8, SD = 7.8. The overall mean age was 24.7, SD = 5.7.

Clinical Measures

During initial clinical assessment demographic and clinical information was collected.

Eating disorder psychopathology was measured using the Eating Disorder Examination (EDE).[29] This is a semi structured diagnostic interview which generates four subscale scores: dietary restraint, eating concern, weight concern and shape concern. The mean of these four subscales produces a global score. EDE interviews were carried out by trained assessors. Inter-rater reliability was checked by second scoring every 10th interview.

Psychosocial impairment was measured using the clinical impairment assessment for EDs (CIA).[30] This is a 16-item questionnaire which generates a single global score to signify level of impairment. Each item is rated on a four-point scale (max score = 48, with higher scores indicating greater impairment).

To investigate whether cluster-group membership was affected by common co-morbid factors additional psychopathology was measured. The Depression, Anxiety and Stress Scale-21 (DASS-21)[31] uses a four-point forced choice severity rating (max score = 63) to indicate greater levels of depression, anxiety and stress. The Obsessive Compulsive Inventory-Revised (OCI-r)[32] assesses distress associated with obsessions and compulsions. The 18-item questionnaire uses a five-point forced choice severity scale and provides a single global score (max score

= 72). The cognitive flexibility scale (CFS)[33] assesses awareness of the availability of alternative thoughts and behaviors in a given situation and the willingness and self-efficacy to enact these options. The questionnaire contains 12 items each rated on a six-point Likert scale and generates a single global score (max score = 72). A higher global score implies greater cognitive flexibility. The Beliefs about Emotions Scale (BaE)[34] contains 12 items and assesses beliefs associated with the unacceptability of experiencing and expressing emotions. Items are rated on a six-point scale; higher scores indicate more negative beliefs about emotions.

Service Use

Past ED service utilization data was collected during initial clinical assessment via patient self-report. Whether or not participants had previously entered hospital inpatient treatment for their ED is reported here.

This study is embedded in a large RCT evaluating outpatient treatments.[28] All study participants were offered 20–30 individual treatment sessions plus add on and follow-up sessions over a one year period. Adherence to study treatment and any additional treatment received was routinely recorded on patients' case record forms. The number of treatment sessions attended is reported here.

Neuropsychological Assessment

Pre-morbid intelligence was estimated using the National Adult Reading Test (NART).[35] Executive function was assessed using the WCST.[36] This task involves matching stimulus cards with one of four category cards according to color (C), shape (S), or number (N). After each trial participants are given feedback (right or wrong) and through trial and error they must derive the matching rule. After 10 consecutive trials, the rule changes. There are up to six attempts to derive a rule and rules shift in the following sequence (C-S-N-C-S-N). Participants are not told that the sorting rule will change or what the correct sorting rule is. The task continues until all 128 cards are sorted irrespective of whether the participant completes all rule shifts. The WCST generates numerous performance indices, however, only perseverative errors, where the participant makes a response in which they persist with a wrong sorting rule, and global score (number of trials administered—[categories complete $\times$ 10]), a measure of global efficiency, will be used here. Set-shifting ability was assessed using the Brixton Spatial Anticipation Test (BSAT).[37] This is a rule attainment task consisting of 56 trials where participants must determine the rule that governs the sequence of a moving dot and thus predict the location of the dot in the next trial. The rule changes a number of times during the test and participants must then detect a new rule. The BSAT generates a score of total numbers of errors made (Max: 54). Visuospatial

constructional ability was measured using the central coherence index of the Rey-Osterrieth Complex Figure Test copy trial (REYCC).[38,39] The REY complex figure was scored using methods described in Booth, 2006,[40] where lower scores indicate a more detailed and fragmented processing style. Emotional ToM (eToM) was measured using the Reading the Mind in Films Task (RMF).[41] This task uses a forced choice format and involves 22 film clips of social scenes. Participants must identify how a given character is feeling by the end of the scene and choose from four words which is the most appropriate match. A glossary of all mental states is provided and one point is scored for each correct answer to give an overall accuracy score (max score = 22).

Procedure

Demographic, clinical and service use data were collected at initial clinical assessment with the ED service. Clinical and neuropsychological assessments were conducted by a researcher trained in administering and scoring all tasks during the RCT baseline assessment. Participants were allowed breaks at any point during testing but task order was not changed. Each participant completed the DASS-21, OCI-r and CFS before attending the research assessment. The task order was EDE, body mass index (BMI) (calculated from weight and height measures [BMI = kg/m^2]), NART, CIA, BSAT, RMF, REY, and WCST. The BSAT and RMF were scored using a standardized scoring sheet. The WCST is scored via the computer program and REYCC was scored by two independent researchers and checked by a third to ensure scoring uniformity.

Analysis

To control for age and gender effects performance scores on the neuropsychological and social-cognitive variables were converted into demographically corrected standardized scores (z scores) using the following age and sex matched published control data: WCST Global score, ($n = 120$, age = 27.4, gender = F),[42] WCST Perseverative Errors %, ($n = 199$, age = 27.7, gender = F),[9] BSAT, ($n = 216$, age = 27.0, gender = F),[10] REYCC,($n = 42$, age = 26.3, gender = F),[11] RMF, ($n = 57$, age = 24.0, gender = F),[43] for each participant.

To aid interpretation of analysis the direction of resulting z scores was standardized, so that for all variables higher scores indicate stronger performance. Additionally, z score outliers across all five neuro- or social-cognitive variables beyond ±3.0 were curtailed to values of +3.0 or −3.0 (depending on direction). This prevents cluster solutions from being influenced by individuals with extreme scores and enables a consistent range to be compared across variables. There were no outliers greater than +3.0 for any variables and the number of cases below −3.0 did not exceed 10%.

A hierarchical cluster analysis, using Wards method of minimum variance with a squared Euclidean distance measure, was conducted to identify clusters of performance across the four neurocognitive variables (WCST Global score, WCST Perseverative Errors %, BSAT, REYCC) and single social-cognitive variable (RMF). Cluster analysis techniques were based on previous similar studies within psychosis or depression.[25,44] Cluster analysis is a classification method to maximize the similarity between participants in one cluster whilst minimizing the similarity between participants in different clusters. Hierarchical clustering is recommended for smaller data sets. This allows clusters to be scrutinized at successive steps until an acceptable number of homogenous groups which best describe the data is reached.

To assess differences in demographic, clinical, treatment adherence, neuropsychological and social-cognitive variables one-way between groups analysis of variances (ANOVA) were carried out using the optimum cluster solution. Post hoc testing using Tukey's HSD was conducted and significance value set at $p \leq .05$ to maximize differences detected between clusters. To evaluate pair-wise comparisons, effect sizes were calculated using Cohen's d (d = mean difference/mean standard deviation). Effect strengths were set at small 0.2, medium 0.5, and large 0.8.

Finally, a confirmatory (standard) discriminant function analysis was conducted to determine which combinations of the neuro- and social-cognitive variables best distinguish the cluster groups and whether these combinations could reliably predict cluster membership.

Results

Cluster Analysis

Inspection of the agglomeration coefficients and dendrogram generated by the cluster analysis suggested an optimum three cluster solution to best distinguish between cases. The resulting clusters consisted of two relatively similar sized groups and one smaller group (Cluster1: $n = 45$, Cluster2: $n = 38$, Cluster3: $n = 17$). **Table 1** shows the cluster groups' mean z scores (curtailed) and standard deviations for neuro-and social-cognitive task performance. Between groups ANOVA determined main effects of cluster group for each variable; and effect size calculations (d) estimate the pairwise cluster-group differences (see **Table 1**). The largest effect sizes can be seen for cognitive flexibility variables. There was no main effect of cluster on REYCC performance. This may be due to the overall poor performance of the entire sample on this task (z score: mean = −1.04, minimum = −3.0, maximum = 0.87) resulting in a lack of variance.

TABLE 1. Mean z scores (standard deviation) for neuro- and social-cognitive variables across clusters with subsequent ANOVA results

	Cluster 1 (*n* = 45)	Cluster 2 (*n* = 38)	Cluster 3 (*n* = 17)	ANOVA F (*p*)	Effect sizes, *d*		
					1vs2	1vs3	2vs3
WCST Global Score	0.53 (0.4)	0.51 (0.5)	−2.21 (1.0)	183.7 (0.000)	0.04	3.9*	3.6*
WCST Perseverative Error %	0.29 (0.5)	0.09 (0.5)	−2.41 (0.9)	147.5 (0.000)	−0.4	3.9*	3.6*
BSAT	0.25 (0.6)	−1.74 (0.9)	−0.11 (1.2)	62.0 (0.000)	−2.7*	0.4	−1.6*
REY CC	−0.83 (0.9)	−1.26 (0.9)	−1.07 (1.0)	2.3 (0.104)	−0.5	0.3	−0.2
RMF	−0.09 (0.9)	0.25 (1.3)	−1.11 (1.2)	8.7 (0.000)	0.3	1.0*	1.0*

WCST: Wisconsin Card Sorting Task; BSAT: Brixton Spatial Anticipation Test; CC: Central coherence; RMF: Reading Mind in Films; ANOVA: Analysis of Variance.
*Denotes post-hoc Turkey HSD significant difference between clusters ($p < 0.05$).

FIGURE 1. Profiles of neuro- and social-cognitive z scores by cluster group
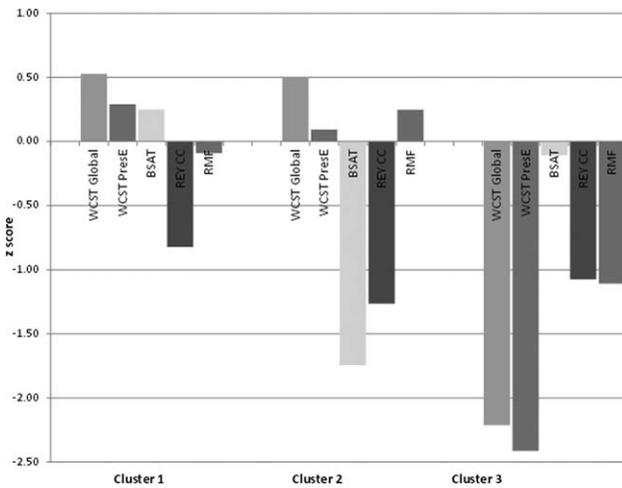
The neuro- and social-cognitive profiles for each cluster are presented in **Figure 1**.

Cluster 1 shows a slight strength in WCST global efficiency and mild weakness in central coherence with average performance on all other variables. Cluster 1 is subsequently labelled "average to high average overall performance." Cluster 2 shows average (z score = ±0.5) WCST perseveration and eToM together with a strength in WCST global efficiency but poor central coherence (REYCC) and BSAT cognitive flexibility. This group can be labelled "mixed performance." In contrast, Cluster 3 shows distinct weaknesses in WCST global efficiency and perseveration, central coherence and eToM but average performance on the BSAT measure of cognitive flexibility. This group can be labelled "poor overall performance."

Demographic and Clinical Characteristics

Table 2 shows mean scores for demographic and clinical measures across the three clusters. ANOVA analysis revealed no significant main effect of clus-

ter for all variables. Effect sizes for all comparisons except NART IQ are in the medium to small range. To confirm IQ did not influence cluster membership Tukey's HSD post hoc comparisons were carried out and revealed no significant differences between cluster pairs ($p > .05$).

Discriminant Function Analysis (DFA)

The neuro- and social-cognitive variables were entered simultaneously as predictors into the DFA. Box's M indicated that the assumption of equality of covariance matrices was violated (Box's $M = 89.5$, $F = 2.7$ $p < .001$). However with larger sample sizes a significant result is not regarded as serious. Following analysis two functions were generated to separate the three clusters. Function 1 accounted for 78.6% of the variance between clusters (Wilk's $\lambda = 0.07$, $p < .001$). Function 2 accounted for the remaining 21.4% of the variance between clusters and was also statistically significant (Wilk's $\lambda = 0.42$, $p < .001$). Inspection of the structure matrix revealed predictors with the following discriminant loading on each function, where 0.3 is seen as the cut off between important and less important variables. In Function 1 WCST global score (0.84) and WCST perseverative errors (0.74) appeared the most important predictors and separated Clusters 1 and 2 from Cluster 3. The BSAT (0.86) appeared to be the most important predictor in Function 2, separating Cluster 1 from Cluster 2. The overall classification rate was Cluster 1 = 92.1%, Cluster 2 = 100% and Cluster 3 = 88.2%. Following cross validation where the "leave one out" method confirmed the stability of this classification procedure the overall correct classification rate was 92%, more specifically Cluster 1 = 86.8%, Cluster 2 = 100% and Cluster 3 = 82.4%. The hit ratio was greater than 25% above that which would be achieved by chance (three clusters would give a 33% chance of correct classification). This suggests the two functions have good predictive accuracy.

TABLE 2. Mean scores (standard deviation) for demographic and clinical variables across clusters and subsequent ANOVA results

	Cluster 1 ($n = 45$)	Cluster 2 ($n = 38$)	Cluster 3 ($n = 17$)	ANOVA F (p)	Effect sizes, d		
					1vs2	1vs3	2vs3
Age (yrs)	24.7 (5.8)	25.1 (6.0)	23.9 (5.1)	0.25 (0.78)	−0.1	0.1	0.2
Illness Duration (yrs)	6.5 (4.9)	8 (6.7)	5.2 (3.1)	1.58 (0.21)	0.3	0.3	0.6
NART IQ	109.6 (7.6)	107.3 (8.1)	104.4 (7.1)	2.88 (0.06)	−0.3	0.7	0.4
BMI (kg/m^2)	16.8 (1.0)	16.7 (1.2)	16.6 (1.4)	0.28 (0.75)	−0.1	0.2	0.1
EDE Global	3.2 (1.3)	3.3 (1.2)	3.8 (1.3)	1.46 (0.24)	0.1	−0.5	−0.4
DASS-21 Total	31.0 (10.8)	32.6 (12.9)	27.0 (14.3)	1.18 (0.31)	0.1	0.3	0.4
CIA Total	32.4 (8.2)	32.6 (7.4)	33.5 (9.8)	0.12 (0.89)	0.02	−0.1	−0.1
CFS Total	48.0 (8.2)	48.7 (9.3)	45.7 (8.6)	0.64 (0.53)	0.1	0.3	0.3
OCI-R Total	21.7 (13.4)	25.6 (14.5)	21.8 (12.0)	0.93 (0.4)	0.3	0.01	0.3
BAE Total	51.5 (12.5)	49.7 (9.1)	49.6 (15.6)	0.26 (0.77)	0.2	0.1	0.008
Treatment Adherence	18.6 (6.2)	18.4 (7.3)	16.3 (7.8)	0.62 (.54)	0.03	0.3	0.3

NART IQ; National Adults Reading Test IQ; BMI: Body Mass Index; EDE: Eating Disorder Examination Interview; DASS-21: Depression Anxiety and Stress Scale-21; CIA: Clinical Impairment Assessment; CFS: Cognitive Flexibility Scale; OCI-r: Obsessive Compulsive Inventory revised; BAE: Beliefs About Emotions Scale; ANOVA: Analysis of Variance.
*Denotes post-hoc Tukey's HSD significant difference between clusters ($p < 0.05$).

Cluster Membership, Clinical, and Demographic Measures and Service Use

The three clusters did not differ significantly in terms of the primary diagnosis of their members [X^2 (4) = 0.61; $p = .96$]. **Table 3** shows that the diagnostic categories are relatively equally distributed across all clusters. There was also no difference between the proportion of cluster-group members who were in a relationship [X^2 (2) = 1.65; $p = .44$]. In addition, cluster groups did not differ significantly in the proportion of group members taking antidepressant medication [X^2 (2) = 1.11; $p = .57$] or the contraceptive pill [X^2 (2) = 2.56; $p = .32$]. Finally, cluster groups did not differ significantly in terms of the proportion of members with previous hospital inpatient admissions for EDs [X^2 (2) = 0.25; $p = .89$] or mean number of treatment sessions attended as part of the large RCT through which individuals were recruited (see **Table 2**).

Discussion

This study aimed to discover whether distinct neuro- and social-cognitive profiles could be identified within a sample of adult female out-patients with AN. Three separate clusters were found, Cluster 1, ("average to high average overall performance") represents 45% of participants and is characterized by a slight strength in WCST global efficiency and mild weakness in central coherence with average performance on all other variables. Cluster 2, ("mixed performance") represents 38% of the participants and shows average WCST perseveration and ToM, a strength in WCST global efficiency but poor central coherence and BSAT cognitive flexibility. Finally, Cluster 3, ("poor overall

TABLE 3. Distribution of clinical and demographic information and service use across cluster groups

	Cluster 1 ($n = 45$)	Cluster 2 ($n = 38$)	Cluster 3 ($n = 17$)
AN-Res %	44.4	42.1	47.1
AN-B/P %	35.6	31.6	29.4
EDNOS-AN %	20.0	26.3	23.5
In a relationship (yes) %	28.2	42.1	35.3
Anti-depressant (yes) %	44.2	39.5	29.4
Contraceptive Pill (yes) %	22.2	28.9	76.5
Previous inpatient admission (yes) %	18.2	21.1	23.5

AN-Res: Anorexia Nervosa restricting subtype; AN/B/P: Anorexia Nervosa binge purge subtype; EDNOS-AN: Eating Disorder Not Otherwise Specified-Anorexia Nervosa subtype.

performance") represents 17% of participants and shows distinct weaknesses in WCST global efficiency, perseveration, central coherence and ToM but average performance on BSAT cognitive flexibility.

Although previous neuro- and social-cognitive literature has found performance deficits across the AN population,[9–11,15] our findings show that there is a high degree of variability in performance. This heterogeneity would be masked if analyzing the sample as a whole. Performance across the three clusters shows a wide range of abilities on all variables with the exception of central coherence. Here, there was no significant difference between clusters; however, this may be due to poor performance across the entire sample.

The appearance of Cluster 3 confirms our hypothesis of an ASD-like subset within the sample. A total of 17 participants fell into this category and demonstrated poor executive function, weak central coherence and difficulties in eToM. These results are consistent with previous research which

suggests that 15–20% of individuals with AN have pre-morbid ASD.[18] In addition, Cluster 2 shows neuropsychological difficulties in set-shifting and central coherence but average eToM. This cluster contains a much larger proportion of the sample, suggesting neurocognitive inefficiencies alone are more widespread within AN. However, it is still unclear whether these impairments reflect pre-existing developmental or illness-acquired difficulties.

The differing patterns of performance on the WCST and BSAT tasks between the three clusters needs to be explored. According to the DFA, WCST performance splits Clusters 1 and 2 from Cluster 3 and differences in BSAT performance separate Clusters 1 and 2. Whilst both tasks measure cognitive flexibility, they differ in terms of complexity and feedback. In the BSAT participants are informed that the sorting rule relates to a number pattern and that the rule will change. In contrast for the WCST, participants are not given any information regarding the sorting rule or pattern changes. Furthermore, the WCST uses written and audio 'right/wrong' immediate feedback whereas the BSAT gives no feedback other than the appearance of the next trial. The BSAT therefore relies on additional processes of remembering the response and matching for correctness, whereas the WCST depends on the cognitive processes of searching for a category and consolidating the correct classification.[9]

Participants in Cluster 3 show poor WCST performance but average BSAT performance. These individuals may therefore be failing to learn from the explicit feedback of the WCST, but performing well on the simple BSAT switching task. This finding falls in line with results from the single study we were able to find which uses the BSAT in an autistic sample. Here, no difference was found between healthy controls and adolescents with High Functioning Autism in terms of number of BSAT errors made.[45] Previous research has shown that individuals with ASD tend to use fewer spontaneous strategies and more idiosyncratic behavior,[46] which may disadvantage them in more open ended tasks such as the WCST. In contrast, individuals in Cluster 2 appear able to integrate and respond to more complex stimuli and learn from feedback but are perhaps less able to utilize memory and response matching to perform well on the BSAT. It appears that poor performance in set shifting and to a lesser extent weaknesses in central coherence creates this middle cluster and prevents the sample from being split into merely good and bad performers.

This neuro- and social-cognitive heterogeneity of the sample appears despite comparable levels of ED and other psychopathology, illness duration and medication use. Individuals with a diagnosis of EDNOS-AN were just as likely to appear in each cluster as individuals with "true" AN. Of specific importance to the social cognition findings is the lack of difference between clusters in terms of oral contraceptive use and relationship status, both of which are often thought to relate to ToM abilities. There is also no effect of BMI or IQ on task performance. Interestingly, self-reported obsessive compulsive behaviors, cognitive flexibility and beliefs about the acceptability of emotions had no relationship with neuro- and social-cognitive task performance. This finding may have important implications for clinical practice as patients may not be aware of their own difficulties. This could increase the chance of problems being missed by the clinical team and therefore not addressed within treatment.

However, an alternative perspective may be that these inefficiencies are "clinically silent" and so are not necessarily effective treatment targets. Therefore, the question as to whether clinical practice will benefit from neuro- and social-cognitive profiling remains.

This study is uniquely able to comment on the 'treatment journey' of participants, by assessing the relationship between cluster-group membership, past service use and current treatment adherence. Results show cluster-group membership has no relationship with past or present service utilization. This finding contrasts with the previously mentioned study of treatment completion in AN inpatients with high versus low ASD traits. In this earlier study a larger but non-significant proportion of individuals with high ASD features were less likely to prematurely terminate their treatment than those with low ASD traits.[24] The authors speculate that individuals with high ASD traits adopt and maintain the rules and routines imposed in an inpatient setting to ease anxieties of the new environment. However, this argument cannot be similarly applied to outpatient treatment; this may explain the lack of significant findings in this study.

This study has several important strengths. Firstly, this is the first study to combine neuro- and social-cognitive task performance clustering in a large sample of adult outpatients with AN. This is also the first clustering study to record diagnostic subtype, use of antidepressant and contraceptive medication and illness duration, therefore allowing these variables to be removed as possible confounds. Cluster-group membership was found to

be unrelated to IQ and efforts were made to control for the effects of extreme scores on clustering techniques. ED and other psychopathology were examined using the same measures across all participants so results are comparable and easy to interpret. Results are also interpreted in relation to widely available age and gender matched control group data. With the exception of WCST Global Score, these control data were also taken from other studies within the authors' department to ensure uniformity in task administration. Finally, this study has the benefit of being imbedded in a large RCT where participants complete the testing battery over multiple longitudinal time points and service utilization is routinely recorded. This has enabled the relationship between cluster-group membership and treatment adherence to be explored and will allow for future investigation into the temporal stability of the clusters identified at baseline within the same sample. It will also allow investigations into whether cluster membership predicts clinical outcomes longitudinally and whether performance deficits relate to malnutrition or remain following weight restoration.

This study also has some limitations. Firstly, it would have been of interest to include a measure of ASD traits to assess whether cluster membership was predictive of self-reported difficulties. Secondly, the testing battery included a single measure of ToM, not a broader set of socio-emotional variables which could have further confirmed the existence of the ASD-like subset. The testing battery was, however administered in the same order across participants and contains several tasks so counterbalance effects, effort and fatigue may have an influence on results. Finally, the cross sectional design and the potential selection bias of help-seeking adult outpatients agreeing to participate in an RCT has the potential to limit the generalizability of these findings. Direction of causality cannot be inferred as it is unknown whether cluster-group membership represents a consequence of AN, or a predisposing factor.

Despite these limitations, this study has some important implications. Firstly, our findings suggest that even with very similar levels of ED and other psychopathology adult outpatients with AN show distinct neuropsychological and social-cognitive profiles. This suggests that many individuals in outpatient treatment for AN show few weaknesses in neuro- and social- cognitive task performance whilst the difficulties of a significant sub-group are more pronounced. Second, as mentioned above the lack of relationship between cluster group, self-report, demographic, and clinical

data raises the debate as to whether these inefficacies are important treatment targets or are clinically silent. It follows that without neuro- and social-cognitive testing, clinicians are unable to gain an understanding of the pattern of deficits within an individual. Future research into the relationship between cluster group and ED recovery will explore the clinical relevance of cluster-group membership. Finally, the DFA results show WCST and BSAT performance are the most important predictors to separate the clusters. Therefore, if clusters are found to be clinically relevant this provides an economical way of distinguishing patients into cluster groups without individuals completing the entire testing battery.

Cluster analysis is an explorative, hypothesis-generating and data driven approach. Thus, analogous to previous studies in the psychosis field,[25–27] replication studies are required in other well-defined AN samples of different illness severity (e.g., inpatients) or stage (e.g., adolescents, or recovered samples), in other ED populations (e.g., bulimia nervosa) and in high risk samples (e.g., offspring of mothers with AN) and in trans-diagnostic ED samples to assess the robustness and specificity of the cluster solutions found here. Moreover, future studies should examine a broad range of collateral validators (neurobiological, developmental, or clinical) to further assess the meaning of our cluster findings and assess their potential utility in characterizing etiological heterogeneity, predicting longer term outcomes or guiding individual tailoring of treatment.

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