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ABSTRACT

Background: Deficits in neuropsychological functioning have consistently been identified in patients with anorexia nervosa (AN). However, little is known on how decision making in AN patients evolves in response to treatment or whether impairments are reversible. **Method:** AN patients (*n*=42) completed the Iowa Gambling Task (IGT) upon admission to a 3-month day-hospital treatment program and at a 1-year follow-up. Patient IGT performance was compared to age-matched controls (*n*=46). **Results:** AN patients displayed poorer performance on the IGT at admission compared to controls ($p<.001$). Patients with full remission (*n*=31; 73.9%) at the 1-year follow-up improved IGT performance ($p=0.007$) and scores were similar compared to controls ($p=0.557$). AN patients with partial/no remission at follow-up (*n*=11; 26.1%) did not improve IGT scores ($p=0.867$). **Conclusions:** These findings uphold that enduring remission from AN can reverse decision-making impairments and they might be most likely explained by clinical state rather than a trait vulnerability.

Keywords: Neuropsychology, Eating and Feeding Disorders, Cognitive Impairments, Longitudinal Studies, Cognitive Behavioral Therapy, Choice Behavior

INTRODUCTION

Neuropsychological studies have repeatedly reported significant impairments in cognitive function in anorexia nervosa (AN). These deficits are specifically present in memory, attentional functions and select executive functions (e.g. decision-making, set-shifting and global processing) (Reville, O'Connor, & Frampton, 2016; Van Autreve et al., 2016; Westwood, Stahl, Mandy, & Tchanturia, 2016). With regards to the psychopathological decision-making profile of AN, individuals with AN persistently opt to restrict food intake in the interest of obtaining an immediate reward – received in the form of relief from anxiety elicited by fear of gaining weight – while disregarding the negative consequences of such behaviors to their physical health (Danner et al., 2012).

The Iowa Gambling Task (IGT) was designed to capture the inability of individuals to make adaptive decisions when presented with complex choices under conditions of uncertainty, reward, and punishment, as well as to functionally asses patients with damaged orbitofrontal cortex (OFC) (Bechara, Damasio, Damasio, & Anderson, 1994). Many studies using the IGT have reported impaired decision-making in currently ill AN individuals (Adoue et al., 2015; Reville et al., 2016), including male patients with AN (Tchanturia et al., 2012), and decreased autonomic response while performing the task (Tchanturia et al., 2007), as is consistent with the Somatic Marker Hypothesis (Damasio, 1996). These deficits are of clinical relevance and numerous models have been developed in which decision-making characteristics contribute to the development and maintenance of AN symptomatology (Treasure & Schmidt, 2013).

As malnutrition causes cognitive impairment independently of the presence of AN, at present the question as to whether cognitive deficits in actively symptomatic AN patients is a consequence of the illness or a preexisting, underlying impairment remains unsettled (Guillaume et al., 2015; Harrison, Tchanturia, & Treasure, 2010). Some research has suggested that decision-making impairments aggregate in AN families and could constitute a candidate endophenotype for AN (Galimberti et al., 2013; Lang, Treasure, & Tchanturia, 2016). On the other hand, other studies uphold the reversibility of decision-making impairments following re-feeding (Lindner, Fichter, & Quadflieg, 2012). Although it must be noted that evaluations of neuropsychological processes in weight-restored AN patients have largely been cross-sectional and thus fail to verify if differences were present during the acute phase of illness (Ely, Wierenga, & Kaye, 2016).

Longitudinal research on decision-making in AN patients has thus far been inconsistent. One study found that AN patients did not significantly improve IGT performance from intake to discharge, though patients with a better decision-making profile at baseline showed greater improvement in nutritional status (Cavedini et al., 2006). On the other hand, Bodell and

colleagues (2014) found that overall IGT performance significantly improved from baseline to weight restoration in a subset of AN patients who were poor performers at baseline. This same study indentified that lower body mass index (BMI) and OFC volume were significantly associated with worse IGT performance, suggesting that these deficits represent a trait-like cognitive vulnerability that contributes to the maintenance of self-starvation behaviors. Nonetheless, the relatively short duration of follow-up in these two studies may not have been able to capture significant, lasting neurocognitive changes.

Aims

Examinations of neuropsychological performance in AN patients have repeatedly revealed significant decision-making impairments (Guillaume et al., 2015). The paucity of studies examining whether such impairments are state- or trait-like warrants longitudinal research comparing decision-making performance in both an acute and recovered state. As such, the primary aim of the present study was to explore IGT performance in AN patients prior to admission to treatment and at a one-year follow-up. A secondary aim of this study was to compare neuropsychological performance between AN patients in full remission, AN patients in partial/no remission and healthy controls (HC).

METHOD

Participants and Procedure

Our study sample comprised 42 women with AN (BMI<18.5 kg/m^2; 28 restrictive subtye, 11 binge-purgative subtype and 3 EDNOS) and 46 female HC (BMI18.5–24.9 kg/m^2). Patients were diagnosed according to DSM-IV-TR criteria (APA, 2000). These diagnoses were reanalyzed and recodified *post hoc* using DSM-5 criteria (APA, 2013). The AN patients in our sample were consecutively recruited from a three-month day-hospital treatment program at Bellvitge University Hospital (Barcelona, Spain). This manualized treatment program targets the nutritional and dietary needs of AN patients and includes daily group cognitive-behavioral therapy (CBT) sessions (Fernández-Aranda & Turon, 1998). Patients were re-evaluated via a face-to-face interview one year following admission to the treatment program and were categorized as: full or partial/no remission. These categories were based on established treatment outcomes in the DSM-5 (APA, 2013). Only patients who completed the day-hospital treatment program and who attended the one-year follow-up assessment were included in our analysis.

The following groups of individuals were excluded from the present analysis: males, individuals under the age of 18, patients with endocrine disorders such as diabetes mellitus, diabetes insipidus and hypo- or hyperthyroidism. The exclusion criteria for the HC group were:

presenting a lifetime history of ED and a BMI below 18.5 kg/m^2 or higher than 25 kg/m^2. This age-matched comparison group was recruited from the local hospital/university community. The study was approved by the Ethics Committee of Bellvitge University Hospital, and signed informed consent was obtained from all participants.

We evaluated ED symptoms via the validated Spanish version of the Eating Disorders Inventory-2 (EDI-2; Garner, 1991). Depression levels were measured using the depression subscale of the Spanish version of the Symptom Checklist-Revised (SCL-90-R; Derogatis, 1994). BMI was measured by bioelectrical impedance analysis.

Decision-making was assessed using a computerized version of the IGT (Bechara, Damasio, Tranel, & Damasio, 1997). In this task, the subject has to select 100 cards, dispersed evenly among five blocks (20 in each block), from four decks (A, B, C and D). A response is given after selecting a card indicating either a gain or loss of money. Two decks (A and B) are not advantageous as the final loss is greater than the final gain. Decks C and D, however, are advantageous as they provide an overall gain. Participants are instructed that the final goal of the task is to accumulate as much money as possible. In order to determine the net score for each block, along with the overall net score, the number of cards selected from decks A and B is subtracted from the number of cards selected from decks C and D [i.e. (C + D) - A + B)]. Higher scores point to better performance while negative scores point to persistently choosing disadvantageous decks. For the one-year follow-up assessment, the task was counterbalanced for which decks were advantageous and disadvantageous.

Data analyses

Data are presented as mean±standard deviation (SD). Analyses were carried out with SPSS20 for Windows. Mixed analysis of variance (ANOVA) compared measures between groups (between-factor with three levels: HC vs AN-partial/no remission and AN-full remission) and time (intra-factor with two levels: admission vs. 1-year follow up). *Post hoc* analysis was based on Sidak adjustment test for multiple comparisons.

Due to the potential association between the variables analyzed in this work and all the comparisons were adjusted for the covariates years of education and depression level at baseline (pre-treatment) in order to avoid potential biases in the results (Abbate-Daga et al., 2015). Effect sizes for pairwise comparisons were estimated through Cohen's-*d* coefficient ($|d|>0.50$ was considered moderate effect size and $|d|>0.80$, large effect size).

RESULTS

Sample characteristics

Groups were age-matched: 28.2±7.2 years for the HC group and 28.8±9.7 years for AN patients (p=0.707). Differences appeared for the means in years of education (17.5±3.3 years for HC versus 15.2±2.9 years for AN; p=0.001) and for scores on the SCL-90-R depression scale (0.75±0.53 for HC versus 1.98±1.01 for AN; p<0.001).

Changes from admission to 1-year follow-up

Table 1 includes the results of the mixed ANOVA with the comparison of pre-post changes between groups, adjusted for the covariates years of education and depression (complete ANOVA results are available in Table S1, supplementary). Figure 1 displays total IGT scores and IGT block scores for each group. At baseline, the HC group presented a higher BMI, lower EDI-2 total scores and better overall IGT performance compared to AN patients.

At the 1-year follow-up, 31 patients (73.9%) presented full remission whereas 11 patients (26.1%) presented partial or no remission from AN. AN patients with full remission and AN patients with partial/no remission presented equal means in all measures, except for EDI-2 total scores (higher levels of eating symptomatology for AN patients with partial/no remission).

At post-treatment, IGT scores for AN patients with full remission were similar to HC scores. AN patients with partial/no remission IGT scores remained lower than HC scores. Both groups presented higher EDI-2 scores and lower BMI compared to HC at the 1-year follow-up.

Regarding the factor time, both AN patients with full remission and AN patients with partial/no remission increased BMI and decreased overall EDI-2 scores. Only AN patients with full remission improved IGT performance.

DISCUSSION

This study compared IGT performance in AN patients with full remission, AN patients with partial/no remission and HC at admission to- and 1-year following treatment.

The findings of this work showed that AN patients performed significantly worse on the IGT than the comparison group at baseline, because they did not improve their execution throughout the task. This result dovetails with previous studies, which have also reported impaired decision-making in currently ill AN women (Fagundo et al., 2012; Tchanturia et al., 2007). Depression is a factor that must be taken into account when examining neuropsychological performance in AN patients as an association between depression levels and autonomic response to positive and negative stimuli has been reported in the literature (Abbate-Daga et al.,

2015). For this reason, the current study controlled for depressive symptomatology when assessing IGT performance.

AN patients with full remission at the one-year follow-up significantly improved IGT scores and did not present any differences in IGT performance compared to HC. The present data support the position that poor decision-making in AN patients is associated with starvation and eating pathology, and that these deficits can be reversed by the restoration of healthy weight and nutritional status. It's worth noting that both patients who achieved full remission and patients with partial/no remission presented equally poor IGT performance at baseline. As such, decision-making impairments may represent a consequence of acute malnutrition for most patients, though for a small portion of individuals, poor decision-making may be a risk factor for AN (Bodell et al., 2014). Our findings also seem to contradict the hypothesis supporting that decision-making impairments constitute a biological marker in AN and that these impairments "precede and persist after the development of AN" (Galimberti et al., 2013). Longitudinal studies are direly needed to determine whether such deficits are present prior to the development of AN and to confirm the trait or state nature of these dysfunctions.

Our findings also seem to contradict the hypothesis supporting that decision-making impairments constitute a biological marker in AN and that these impairments 'precede and persist after the development of AN' (Galimberti et al., 2013). Other studies have provided evidence of similar biological markers in OCD (Cavedini, Zorzi, Piccinni, Cavallini, & Bellodi, 2010). However, an association between clinical severity and decision-making impairment has yet to be established (Cavedini et al., 2002). In this same vein, similar discrepant results have emerged when examining other aspects of decision making such as delay discounting. For example, Decker, Figner, and Steinglass (2015) found that AN patients showed a preference for delayed over earlier rewards but that after weight restoration, these differences ceased to be significant. Another study, however, failed to find any differences in delay discounting between patients with AN, weight-recovered AN patients and patients after short-term weight restoration (Ritschel et al., 2015). Longitudinal studies are direly needed to determine whether such deficits are present prior to the development of AN and to confirm the trait or state nature of these dysfunctions (Lindner, Fichter & Quadflieg, 2014).

Limitations and Future Research

The findings of this study should be considered with certain caveats in mind. First, our study did not examine the effects of disorder duration on decision-making performance and it has been postulated that prolonged malnutrition may have a permanent scarring effect on frontal lobe function (Joos et al., 2011). Relatedly, one recent study found that impairments in executive functioning in bulimia nervosa patients with a history of AN were more pronounced than in

patients without (Degortes, Tenconi, Santonastaso, & Favaro, 2016). Second, a greater sample size would have allowed for the identification of predictors of treatment response for patients who achieved full remission and for patients with partial/no remission. Such information could prove to be valuable in developing tailored treatment plans for AN patients. Third, we did not compare IGT performance between AN patients with restrictive and binge-purge subtypes. Differential impairments underlying IGT performance in these two subtypes have been identified though no study to date has compared their response to treatment (Chan et al., 2013). Finally, it would have been of interest to measure the evolution of autonomic skin conductance response (SCR), being that significantly attenuated SCR has been associated with decision-making ability (Tchanturia et al., 2007).

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TABLE 1

Mixed ANOVA adjusted for years of education and SCL-90-R depression scores

	Mean (adjusted)						Factor: group (*p-value)*						Factor: time (*p-value)*		
	HC*; n=46*		AN-I*; n=11*		AN-F; *n=31*		HC vs AN-I		HC vs AN-F		AN-I vs AN-F		Pre vs Post		
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	HC	AN-I	AN-F
BMI (kg/m^2)	21.0	21.4	16.4	18.8	16.7	19.1	**<.001*†**	**.001*†**	**<.001*†**	**<.001*†**	.668	.698	.143	**<.001*†**	**<.001*†**
EDI-2 total score	23.3	21.0	91.9	62.6	61.7	41.7	**<.001†***	**<.001*†**	**<.001*†**	**<.001*†**	**.004*†**	**.015*†**	.546	**<.001*†**	**<.001*†**
IGT measures															
Total Score	28.9	22.4	-2.33	-0.71	3.20	17.9	**.003*†**	**.047†**	**<.001*†**	.557	.532	.064†	.169	.867	**.007*†**
Block 1	-1.84	-1.85	-3.08	-0.63	-1.98	0.15	.629	.647	.930	.253	.625	.734	.989	.367†	.161
Block 2	4.92	5.14	0.43	1.39	0.76	3.02	.142†	.228†	**.039*†**	.299	.901	.547	.875	.736	.161
Block 3	9.08	5.55	-1.02	-1.15	0.23	4.72	**.001*†**	**.050†**	**<.001*†**	.712	.633	**.049*†**	**.039**	.971	**.022*†**
Block 4	9.54	7.57	1.04	1.04	2.32	4.69	**.018*†**	**.048†**	**.002*†**	.193	.677	.213†	.267	.999	.244
Block 5	7.17	6.37	0.30	-1.34	1.86	5.38	.096†	**.030†**	**.050*†**	.665	.661	**.030*†**	.662	.661	.096

Note. SD: standard deviation. |*d*|: Cohen's-d measuring effect-size.

HC: healthy controls. AN-I: anorexia with incomplete (partial/no) remission. AN-F: anorexia with full remission. BMI: body mass index. IGT: Iowa Gambling Task.

*Bold: significant comparison (.05 level). †Bold: effect size in the moderate (|*d*>0.50) to good range (|*d*|>0.80).

TABLE S1-supplementary

Mixed ANOVA adjusted for years of education and SCL-90-R depression scores

	Mean (adjusted) and standard deviation												F.group: HC vs AN-I				F.group: HC vs AN-F				F.group: AN-I vs AN-F				F.time: Pre vs Post					
	HC; *n=46*				AN-I; *n=11*				AN-F; *n=31*				Pre		Post		Pre		Post		Pre		Post		HC		AN-I		AN-F	
	Pre		Post		Pre		Post		Pre		Post		*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|	*p*	|*d*|
BMI (kg/m^2)	21.0	2.16	21.4	2.63	16.4	1.06	18.8	2.69	16.7	0.96	19.1	1.50	**<.001***	**2.67†**	**.001**	**0.95†**	**<.001***	**2.56†**	**<.001***	**1.04†**	.668	0.26	.698	0.14	.143	0.15	**<.001***	**1.16†**	**<.001***	**1.93†**
EDI-2 total score	23.3	18.5	21.0	16.9	91.9	38.2	62.6	36.5	61.7	36.5	41.7	27.7	**<.001***	**2.29†**	**<.001***	**1.46†**	**<.001***	**1.33†**	**<.001***	**0.90†**	**.004***	**0.81†**	**.015***	**0.64†**	.546	0.12	**<.001***	**0.78†**	**<.001***	**0.62†**
IGT measures																														
Total Score	28.9	28.2	22.4	33.2	-2.33	20.8	-0.71	16.8	3.20	20.5	17.9	25.0	**.003***	**1.26†**	**.047**	**0.88†**	**<.001***	**1.04†**	.557	0.15	.532	0.27	.064	**0.87†**	.169	0.21	.867	0.09	**.007***	**0.64†**
Block 1	-1.84	7.06	-1.85	6.66	-3.08	5.83	-0.63	3.56	-1.98	3.54	0.15	6.13	.629	0.19	.647	0.23	.930	0.03	.253	0.31	.625	0.23	.734	0.16	.989	0.00	.367	**0.51†**	.161	0.43
Block 2	4.92	9.00	5.14	8.09	0.43	5.68	1.39	2.24	0.76	3.67	3.02	7.10	.142	**0.60†**	.228	**0.63†**	**.039***	**0.60†**	.299	0.28	.901	0.07	.547	0.31	.875	0.03	.736	0.22	.161	0.40
Block 3	9.08	8.70	5.55	9.32	-1.02	5.02	-1.15	5.80	0.23	4.68	4.72	6.96	**.001***	**1.42†**	**.050**	**0.86†**	**<.001***	**1.27†**	.712	0.10	.633	0.26	**.049***	**0.92†**	**.039**	0.39	.971	0.02	**.022***	**0.76†**
Block 4	9.54	8.79	7.57	9.86	1.04	7.97	1.04	2.50	2.32	7.48	4.69	7.44	**.018***	**1.01†**	**.048**	**0.91†**	**.002***	**0.88†**	.193	0.33	.677	0.17	.213	**0.66†**	.267	0.21	.999	0.00	.244	0.32
Block 5	7.17	10.3	6.37	9.77	0.30	8.96	-1.34	8.55	1.86	9.80	5.38	7.16	.096	**0.71†**	**.030**	**0.84†**	**.050***	**0.53†**	.665	0.12	.661	0.17	**.030***	**0.85†**	.662	0.08	.661	0.19	.096	0.41

Note. SD: standard deviation. |*d*|: Cohen's-d measuring effect-size.

HC: healthy controls. AN-I: anorexia with incomplete (partial/no) remission. AN-F: anorexia with full remission. BMI: body mass index. IGT: Iowa Gambling Task.

*Bold: significant comparison (.05 level). †Bold: effect size in the moderate (|*d*>0.50) to good range (|*d*|>0.80).

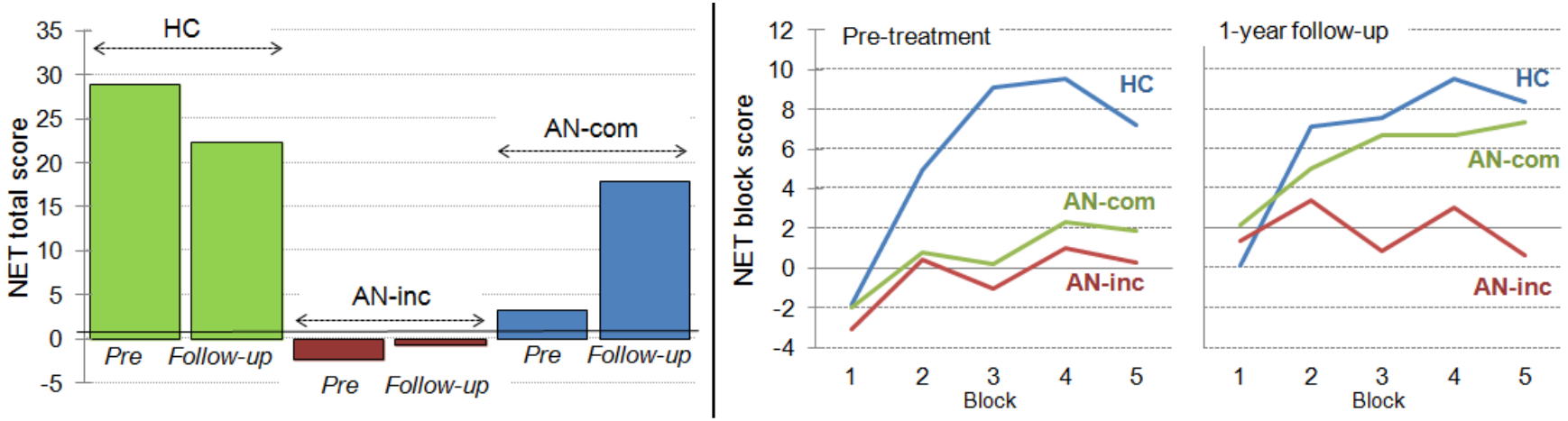

Fig.1. Mean total Iowa Gambling Task scores (*left panel*) and mean Iowa Gambling Task block scores (*right panel*) for each group. Means adjusted for the covariates years of education and SCL-90-R depression scores.

HC: Healthy controls; AN-inc: Anorexia nervosa patients with no/partial (incomplete) remission; AN-com: Anorexia nervosa patients with full (complete) remission.