Exploring the impact of multisensory integration and episodic memory with machine learning: a proof-of-concept study in anorexia nervosa

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Abstract

In addition to established body image alterations, abnormal perception and executive functioning in anorexia nervosa (AN), neurocognitive factors including multisensory integration (MSI) and episodic memory (EM) might play a pivotal role in the diagnosis of this disorder. According to the allocentric lock theory, deficits in the updating of distorted memory of body-based episodes through misleading real-time multisensory bodily stimuli could lead to altered body image in AN. In this study, 25 healthy females and nine AN individuals were tested on a set of neurocognitive measures, encompassing unimodal perceptual accuracy and MSI (MSI) ability assessed with the sound-induced flash illusion (SiFI), episodic memory recognition (EMR) evaluated with a remember/know (R/K) task, memory and executive functions tested with the RBMT-3 and the Stroop task. Collected data were analyzed with Bayesian statistics and machine learning algorithms. In the SiFI task, we found that AN compared to control group had lower discrimination accuracy for unimodal visual and auditory stimuli, for bimodal (visual and auditory) stimuli and disrupted MSI ability. Further, we found on the EMR task and the RBMT-3 that AN individuals had higher proportions of false memories than healthy females. Additionally, we found lower inhibition at the Stroop task for the patient group compared to controls. The importance of the considered neurocognitive measures was confirmed by a machine learning feasibility analysis, which showed that SiFI, RBMT-3, Stroop and EMR had more weight than classic eating disorder risk scales of the EDI-3 when computing classification between the AN and control individuals. In conclusion, MSI along with memory could be crucial factors for improving diagnosis and consequently design innovative therapeutic solutions that tap critical bodily and cognitive elements altered in AN with new technologies such as virtual reality.

Keywords: anorexia nervosa, multisensory integration, episodic memory, diagnosis, allocentric lock theory

1. Introduction

A distorted body image is a core and persistent symptom in anorexia nervosa (AN) that plays a crucial role in the initiation, persistence and relapse of the disease (Dakanalis et al., 2016). Despite exhibiting normal general perceptual abilities (Smeets & Panhuysen, 1995; Smeets, Smit, Panhuysen, & Ingleby, 1997) individuals with AN both feel and see themselves as large-bodied (Case, Wilson, & Ramachandran, 2012). This phenomenon is referred as body image disturbance (BID) (Cash & Deagle III, 1997), in which the actual shape and size of the body do not match the picture patients think they have. BID is a multidimensional construct commonly divided in two key components: perceptual and cognitive-affective (Cash & Deagle III, 1997). The perceptual dimension concerns the overestimation in terms of body size and weight (Gardner & Brown, 2014), while the cognitive-affective component is associated with dysfunctional cognitions and emotions relating to the body (Carey & Preston, 2019). Traditionally, the perceptual component of BID in AN has been primarily investigated looking at visual perception (Gardner & Brown, 2014) and by means of self-report clinical measures such as the eating disorder inventory (Garner, 2004). Several studies indicated that a dysfunctional visuo-perceptual ability may underpin distorted body perception in AN (Brooks, Funk, Young, & Schiöth, 2017). Neurocognitive factors that could lead to altered body image in AN are primarily in relation to executive functioning and visual-spatial functioning (Allen et al., 2013; Darling, Uytman, Allen, Havelka, & Pearson, 2015; Kucharska, Kulakowska, Starzomska, Rybakowski, & Biernacka, 2019; Lopez et al., 2008; Talbot, Hay, Buckett, & Touyz, 2015). In particular, impaired aspects of executive functioning include inhibition, but not impulsivity, for AN restrictive type (Claes, Nederkoorn, Vandereycken, Guerrieri, & Vertommen, 2006; Yue et al., 2020). A way to assess inhibition and impulsivity can be assessed by means of the neuropsychological Stroop color and word test (Scarpina & Tagini, 2017). Currently, Stroop task variations has been used in AN to assess cognitive or emotional components of inhibition and impulsivity (Fassino et al., 2002; Léonard, Divac, Bichindaritz, Rouer-Saporta, & Samuel-Lajeunesse, 1997; Mendlewicz, Nef, & Simon, 2001). However, recent neuroscientific research has revealed other neurocognitive alterations in AN, such as the ability to integrate different multiple sensory domains and altered memory.

Multisensory integration (MSI) refers to how the brain integrates different streams of incoming information from different senses presented in the same space-time context into a coherent and uniform percept, namely the body matrix (Moseley, Gallace, & Spence, 2012; Riva, 2018). The constructed body matrix enables us to make correct predictions using the stored information about the body from conceptual (i.e., the meaning attributed to the body), perceptual (i.e., the size and the shape of the body), and episodic (i.e., the autobiographical events related to the experience of the

body) (Blanke, 2012; Riva, 2018; Riva & Dakanalis, 2018). Recent studies (Riva, 2012; Riva & Gaudio, 2012, 2018) suggest that an impairment in this predictive process, such as altered feedback from and toward the body matrix, could be involved in the etiology of AN. Specifically, the allocentric lock theory (ALT) indicates that AN could be the outcome of an altered MSI linked to how expected (the prediction process) versus experienced body experiences are integrated (Riva & Dakanalis, 2018; Riva & Gaudio, 2012, 2018). Some studies have revealed alterations in AN within several sensory domains, including tactile perception (Keizer, Smeets, Dijkerman, Van Elburg, & Postma, 2012; Keizer et al., 2011), proprioception (Carey & Preston, 2019; Case et al., 2012; Epstein, 2001; Guardia, Cottencin, Thomas, Dodin, & Luyat, 2012; Scarpina et al., 2016), interoception (Badoud & Tsakiris, 2017; Demartini et al., 2017; Di Lernia et al., 2018; Khalsa et al., 2015; Martin, Dourish, Rotshtein, Spetter, & Higgs, 2019; Pollatos et al., 2016). Moreover, it is also known that eating disorders showed deficits in the integration of multiple sensory inputs.

Alterations in MSI amongst AN have been observed using multisensory illusions. The most studied of these paradigms is the well-known rubber hand illusion (RHI), in which individuals typically experience ownership over a fake rubber hand when it is stroked synchronously with their own hand, which is hidden out of view (Botvinick & Cohen, 1998). During the RHI Keizer, Smeets, Postma, van Elburg, and Dijkerman (2014) found that individuals with AN showed a stronger experience of ownership over the rubber hand in comparison to healthy controls. This result implies that patients were more readily to accept inaccurate bodily information to be valid (*“it is my hand”*) after comparing visual and postural aspects of the rubber hand to their internal stored models of the body. In other words, AN subjects assign more weight to external visual inputs compared to stored internal bodily information, rendering the representation of their body more malleable (Case et al., 2012; Eshkevari, Rieger, Longo, Haggard, & Treasure, 2012, 2014; Grunwald et al., 2002; Zopf, Contini, Fowler, Mondraty, & Williams, 2016). Case et al. (2012) through a size-weight illusion battery, evaluate visual and proprioceptive information in AN subject. The authors found a decreased ability in the integration of visual and proprioceptive information in AN subject compared to healthy controls (HCs) that could lead to a distorted body perception. Similarly, Engel and Keizer (2017b) found that AN subject showed larger overestimations on the visual size Estimation task compared to HCs. Furthermore, Grunwald et al. (2002) showed deficits in haptic perception and tactile-visual integration in AN subject, as well as diminished parietal activation during a task, suggesting proprioceptive integrative deficits in the parietal lobes.

Similarly, Mohr et al. (2010) through an fMRI investigation of body size estimation in AN, found evidence that the overestimation in AN may be related to issues with the retrieval of a multimodal representation of the body. These findings indicate that difficulties with the retrieval of past stored

bodily models might also reflect disturbances in body representation. This evidence suggests also that parietal dysfunctions could be connected to body schema disturbances and that these kinds of alterations can also induce deficits in spatial memory (Cipolletta, Malighetti, Serino, Riva, & Winter, 2017; Malighetti, Serino, Riva, & Cipolletta, 2016). In accordance with the ALT, egocentric and allocentric spatial frames of reference play a critical role in updating egocentric multisensory inputs and storing episodic memories related to the body (Riva & Dakanalis, 2018; Riva & Gaudio, 2012, 2018). Indeed, recent research shows that by altering our MSI is possible to modify episodic memory (EM). For instance, the subjective experience of having a virtual body compared to the no-body condition can improve EM in virtual scenarios (Bréchet et al., 2020; Bréchet et al., 2019) or by altering the first-person perspective with virtual reality it is possible to induce amnesia for previously encoded event (Bergouignan, Nyberg, & Ehrsson, 2014). Indeed according to recent studies, AN were found to have impaired memory at neuropsychological testing and also for personal episodes (Malighetti et al., 2016; Nandrino, Doba, Lesne, Christophe, & Pezard, 2006; Riva, 2012; Serino et al., 2015; Weider, Indredavik, Lydersen, & Hestad, 2015). EM is a neurocognitive system that enables the conscious recollection of personally encoded events associated with their spatiotemporal, emotional, perceptual and self-related details (Souhay, Guillery-Girard, Pauly-Takacs, Wojcik, & Eustache, 2013; Tulving, 2001). Whether the episodes are internally or externally cued, they can be recalled according to two types of recognition memory: recollection and familiarity. Recollection occurs when a stimulus gives rise to event/item recall, whereas familiarity is a feeling of memory for the cue without recollection (Montaldi & Mayes, 2010). Hence, recollection happens when we remember in detail an item or an episode, familiarity occurs when we know we encountered the item or experienced the event without a details (Migo, Mayes, & Montaldi, 2012). Recollection and familiarity are related to distinct memory systems (episodic and semantic memory respectively), visual imagery of event (first-person/field and third-person/observer perspectives), spatial frames of reference (egocentric and allocentric) and state of consciousness (autonoetic and noetic consciousness), where episodic recollection is uniquely characterized by the subjective feeling of traveling back in time (Crawley & French, 2005; Montaldi & Mayes, 2010; Piolino et al., 2006; Riva, Di Lernia, Serino, & Serino, 2020). Recognition memory can be assessed with different tests or tasks with ecological or experimental stimuli. The most used standardized neuropsychological test to assess everyday life EM is the Rivermead behavioral memory test (Wilson, Cockburn, & Baddeley, 1985), whereas experimentally the recollection/familiarity paradigm is one of the most used techniques to evaluate recognition processes of EM (Migo et al., 2012).

Despite the cruciality of MSI process and EM, there are still few researches that investigated new neurocognitive features of AN, including MSI and EM in addition to well-known deficits of BID, perceptual and executive functioning. We conducted a preliminary study (Chirico et al., 2019), in which we investigated MSI process of audio-visual stimuli in AN using the sound-induced flash illusion (SiFI). The SiFI is an MSI task that taps temporal aspects of audio-visual integration that have been linked to executive/frontal functioning (Martínez-Sanchis, 2014; Nowak et al., 2016; Romanski & Hwang, 2012) and to a network that include also occipital, parietal and temporal regions that contribute to correct temporal MSI of the stimuli (Hirst, McGovern, Setti, Shams, & Newell, 2020). The temporal aspects of the SiFI task are particularly relevant in the context of AN because it has been showed that temporal binding window of multisensory stimuli are linked to body representation and embodiment paradigms such as the RHI (Costantini et al., 2016; Finotti, Migliorati, & Costantini, 2018; Greenfield, Ropar, Smith, Carey, & Newport, 2015; Greenfield, Ropar, Themelis, Ratcliffe, & Newport, 2017; Rossetti et al., 2020). Despite its cruciality, to our knowledge there is no literature exploring temporal binding in AN. In our study (Chirico et al., 2019) auditory and visual stimuli were presented at different stimulus-onset asynchronies (SOAs) (i.e., temporal discrepancies between the onset of the visual and of the auditory stimuli). Participants were involved in a temporal discrimination task, thus evaluating the integrity of the temporal MSI brain processes (see Materials for accurate SiFI task explanation). Results showed that AN individuals, compared to HCs, gave less accurate responses than controls for each SOA, especially for longer SOAs, and for each sensory modality (visual, auditory and bimodal). Specifically, according to our previous study (Chirico et al., 2019), we hypothesized that anorexics subjects show impairments in temporal discrimination processing of visuo-auditory stimuli compared to healthy controls and alterations in the EM and inhibition compared to HCs. Bayesian statistics was applied to confirm evidence in favor of the presence of alternations (H1) against the evidence of the absence of deficits (H0) in AN compared to HCs. Finally, we explored and discussed the implications of using well-established and innovative neurocognitive factors implicated in the diagnosis of AN by means of machine learning (ML) classifiers.

2. Methods

2.1. Participants

A total of 25 healthy females (mean age = 25.08 years, SD = 1.78; mean education = 17 years, SD = 1; mean BMI = 21.89 kg/m², SD = 2.83) and 9 AN patients (mean age = 30 years, SD = 10.46; mean education = 13.22 years, SD = 0.67; mean BMI = 15.95 kg/m², SD = 1.96). Patients with AN were diagnosed according to DSM-5 and were categorized as restrictive type (American Psychiatric

Association, 2013) by a licensed psychiatrist. Participants in both groups were eligible to take part in the study if they were females, had more than 18 years of age, and had normal or correct-to-normal visual and hearing. Participants in AN group were also required to not have a current or prior history of a neurological disease or psychiatric comorbidity (as assessed SCID-PD-5 (First, 2016). Individuals in control group were required to have a BMI between 18.5 and 25 kg/m² and not to have a current or prior history of psychiatric illness (as assessed by the mini-international neuropsychiatric interview (MINI) (Rossi, 2004)

No missing data was reported, and any participants were removed from the analyses. All subjects provided their written informed consent to the study. The study was approved by the Ethical Committee of Spedali Civili of Brescia for the AN group and the Ethical Committee of the Catholic University of the Sacred Heart of Milan for the control group. Table 1 shows demographic and clinical group differences.

2.2. Materials

2.2.1. Neurocognitive tasks

2.2.1.1. *Sound-induced Flash Illusion (SiFI) Task*

SiFI task (Setti, Burke, Kenny, & Newell, 2011; Setti et al., 2014; Shams, 2000) is an illusion that is induced by audio stimuli presented asynchronously, the procedure allows to evaluate the temporal binding window of audio-visual stimuli by means of SOAs. This binding mechanism enables to perceive as unitary two different sensory inputs instead of distinct percepts. The task induces the individual to see two visual stimuli (e.g., white dots) instead of only one. The task was administered with Presentation (version 17.1) software and aimed at assessing unimodal and bimodal discrimination abilities and integrity of MSI system. It consisted of 94 trials of audio-visual stimuli. The audio is a constant-frequency beep (3500 Hz) and the visual stimuli are white circles (60 x 60 pixels). Individuals were asked to judge whether the stimuli/stimulus presented were/was one or two by pressing '1' or '2' keys. Once answered, participants pressed the space bar to see the next trial, which was preceded by a fixation cross at the centre of the screen. A set of eight training trials was presented at the beginning. In the case of visual and auditory unimodal discrimination abilities, two separates white circles or beeps were presented, for bimodal discrimination abilities two with dots paired with two beeps were and finally for the SiFI two sounds and one white dot were randomly paired with the first or the second beep to induce the MSI illusion. In the present study, we only computed total performances regardless SOAs (70, 110, 150, 230ms) between the two stimuli, as this information is analysed in (Chirico et al., 2019). Twenty-four SiFI (one white dot + two beeps), visual (two white dots) and bimodal (two white dots + two beeps) stimuli were

randomized (six for each SOA). Further six single visual unimodal and bimodal stimuli were randomized as well. Unimodal auditory discrimination performances were assessed separately at the end, with eight pairs of audio stimuli (two for each SOA) and two single beeps randomly presented.

2.2.1.2. Episodic Memory Recognition (EMR) Task

We created a remember (R) and know (K) paradigm based on recollection and familiarity memory (Migo et al., 2012) in order to assess EMR in the two groups. Thirty neutral photos of episodic scenes (e.g., people talking at the bar, woman speaking at the phone) from the international affective picture system (Lang, 1995) were selected according to close to the mean (i.e., neutral rating according to Lang's scoring) values for valence, arousal and dominance. Images were further divided into two sets composed of 15 stimuli randomly paired with or without a sound (unifrequential 570 Hz) of 2 seconds. Intra-stimuli interval was 1 second (centred fixation cross) and presentation time was 2 seconds (Potter, 2012; Wright, 2007). Individuals were only asked to pay attention to the stimuli (incidental encoding). After this encoding phase, participants read for 5 minutes an article about dinosaurs. In the retrieval phase a picture representing a detail taken from the central area of the scene was presented (size: 200 x 150 or 256 x 192 pixels, depending on the orientation of the original image). Details presentation was randomized in each session and predetermined according to a random choice selection (a rectangular shape was drawn and further divided in 4 rectangles numbered 1 to 4 and selected with randomizer.org). Participants were asked to judge if, from that picture, they could recall the rest of the scene in a detailed manner (R), if they know they saw the detail but cannot recall the scene (K) or do not recall anything (forgetting; N) by clicking relevant options under the detail presented. All the 30 images were presented without any distractors. If they answered R or K, they were asked whether they recalled if the image was paired with a sound or not (source memory; (Migo et al., 2012)). If the answer was R, they were asked to provide a detailed description of the episode that must contain the subject, the action or the place and further details if retrieved (experimenters checked the presence or distortion according to a predetermined grid of each required feature/s to be recalled). Two experimenters (C.T. and M.M.) briefly described separately each picture and description were resolved through consensus for the minimum criteria to rate a R memory as correct. If the description did not satisfy these criteria R responses were recorded as R false memories.

2.2.2. Neuropsychological and psychological tests

2.2.2.1. *Eating Disorders Inventory 3 (EDI-3).*

Italian version of the eating disorder inventory-3 (EDI-3) (Giannini, Pannocchia, Grave, & Muratori, 2008) was administered to both groups. For the purposes of the study, we only looked at the drive for thinness (DT), bulimia (B), body dissatisfaction (BD) and the eating disorder risk composite score (EDRC) subscales.

2.2.2.2. *Rivermead Behavioral Memory Test - Third Edition (RBMT-3)*

The Italian version of the RBMT-3 (Beschin, 2013) is an ecological memory test standardized in individuals from 16 to 90 years old, composed of 14 subtests. In our study we only used the face recognition subtest, which consisted of an encoding phase where the individual has to say whether the subject presented is man or woman and if he/she has more or less than 40 years (total of 15 faces). After 5 minutes, delayed recognition was assessed among target and distractor faces (total of 15 faces). Correct recognition and false alarms were recorded.

2.2.2.3. *Stroop Test*

A computer version of the Stroop test (Caffarra, 2002) was administered in order to assess inhibitory (errors) and impulsivity (reaction times; RT) performances in the groups. These parameters were calculated with the same formula [$\text{interference task score} - (\text{denomination task score} + \text{reading task score})/2$] for number of errors and RT. The task was created with Neuropsychia (Makowski & Dutriaux, 2017) with Python (version 3.7). A set of 20 stimuli was created in each subtest. For the denomination part, the participants have to look at the stimuli ('XXX') and answer with coloured buttons (red, blue, green) according to the colour of the stimulus presented. In the reading part, colour words ("red", "blue", "green" in black ink) were shown and the individual had to respond with buttons according to the meaning of the word displayed. In the interference part, the task was to identify the ink with which the word was written and respond with the relevant button. Stimuli were randomized in each session.

3. Procedure

After reading and signing the consent form, participants were seated at 40 cm from a 13-inch PC (Alienware Gaming laptop 7th Gen Intel® Quad Core™ H-Class processors and NVIDIA GeForce® GTX 10-Series) in a quiet room with constant environmental features. The experimental session lasted 45 minutes and was standardized across the participants. First, they were administered the training SiFI task and the task itself; afterwards, the EMR encoding task was administered with 5 minutes interference; thereafter the EMR retrieval phase was carried out. Later, the face encoding recognition subtest was done, within the 5 minutes of interference, the Stroop test

was done and then the face recognition was performed. Lastly, the EDI-3 (MINI for the controls only) were filled out. Debriefing and answers to questions were provided at the end of the session.

4. Data Analysis

In order to carry out demographic, clinical and neurocognitive analyses, we used Bayesian statistics due to small and imbalanced group sizes and in order to find out any interaction effects or equivalences in the performances hardly performable with robust or non-parametric analyses (Leys & Schumann, 2010). Additionally, we tested the feasibility for a ML classification procedure to explore the role of the AN diagnosis predictors (SiFI, EMR, RBMT-3, Stroop, EDI-3 aforementioned measures) collected in our study on the two groups. R version 3.6.2 (R Core Team, 2014) was used to perform the analyses. Indices of Bayesian effect are the median of the posterior distribution of the observed data, the probability of direction (PD), which shows similar behavior as p-value and the effect direction (positive or negative respect to posterior's median sign), the region of practical equivalence (ROPE) and the Bayes factor (BF), which show respectively magnitude of the effect and relative evidence for hypothesis testing (Makowski, Ben-Shachar, Chen, & Lüdecke, 2019). Makowski et al. (2019) reporting rules of thumb were adopted for PD (>97.5% for direction effect existence, which mimic a p-value of .05) and ROPE (< 1% significant effect and > 99% negligible effect). BF evidence for H1 or H0 follow Jeffreys's guidelines (Ly, Verhagen, & Wagenmakers, 2016). Results that satisfied these three indices cut-offs were considered statistically relevant. In addition 89% credible intervals (CI) are computed, which resemble the frequentist confidence intervals and posterior's median is given to show direction of the effect (Makowski et al., 2019). In our analyses, the reference group is AN, therefore positive and negative effects are relative to this group. Weakly informative priors were set as default for all the analyses. For this cluster of analyses *rstanarm* (Goodrich, Gabry, Ali, & Brilleman, 2018), *bayestestR* (Makowski & Lüdecke, 2019) and *emmeans* (Lenth, 2018). R packages were used. All the variables from the EMR were expressed as performance proportions (given responses/maximum of possible answers) for each R/K/N (30 is the maximum responses for each type), R source/K source (the maximum of possible answers is given by the total of R/K responses) and R false memory variables (the maximum of possible answers is given by the total of R responses) and SiFI task responses were expressed as accuracy proportions (correct answers/total) for SiFI, visual, auditory and bimodal, hence a value of zero represents the lowest accuracy and a value of one the best performance. We applied Bayesian linear mixed effects models (5000 iterations with participants as random effect to account for intrasubject variability) and used the values extracted from the EMR task as dependent variable and the group, sound and the given response (e.g., R/K/N/ or R source/K source) as fixed

factors. Bayesian t-test were applied for R false and all the SiFI task total performances as dependent and group as independent variable.

Concerning ML, *caret* (Kuhn, 2008) and *pROC* (Robin et al., 2011) packages were used. Classification algorithms such as support vector machine (SVM radial kernel) and k-nearest neighbors (k-NN) were used as they can be used when dealing with unbalanced classes (Wah, Rahman, He, & Bulgiba, 2016). We used the group as target variable and the other relevant collected variables as predictors (see next paragraph for ML set-up). We excluded from all the analyses single stimulus discrimination performances as healthy groups showed ceiling effect and results were discussed elsewhere (Chirico et al., 2019).

4.1. Machine Learning Classifiers Set-Up

Training set was composed of 60% of the initial observations, whereas the test set was formed of 40% of the data (Boehmke & Greenwell, 2019). Two splits (Kuhn & Johnson, 2013) of the training and test set were created, hence algorithms were tested twice on both cluster of datasets to counterbalance for small sample sizes and assure findings stability. Training and test sets were pre-processed (Boehmke & Greenwell, 2019; Kuhn & Johnson, 2013) by centering and scaling the variables, Yeo-Johnson transformation was applied to reduce skewness and highly correlated (EDRC and bimodal total performance removed, threshold set at $> .95$) and near-zero variance variables (zero predictors removed) were checked. We excluded age and education from this analysis as we are interested in neurocognitive and clinical factors. Classification performance metrics (Boehmke & Greenwell, 2019; Kuhn & Johnson, 2013) were accuracy and receiver operating characteristic (ROC). Suggested (Boehmke & Greenwell, 2019) resampling method for the training of the algorithms was a 10-fold cross-validation (CV) repeated 5 times.

Hyperparameters tuning for the algorithms was set with 5 possible values (i.e., maximum of 5 k for NN and 5 sigma and C value for SVM radial). Confusion matrices for the two algorithms were computed on the 40% of the test sets.

5. Results

5.1. Demographics and Clinical Characteristics

Table 1 shows demographics and psychological analyses of the two groups with Bayesian t-tests. In addition, we looked at differences in the Stroop test and the RBMT-3. For the errors at the Stroop, there is moderate evidence ($BF = 3.46$), in favor of the presence of the effect of the pathology, which has a probability of 98.15% (PD) of being positive (median = 0.68, 89%CI[0.16,1.22]) and significant (0% in ROPE), where AN patients made more errors (mean = 0.89, SD = 1.36) than the control group (mean = 0.04, SD = 0.61). For the RBMT-3, there is very strong evidence ($BF =$

64.97), in favor of the presence of an effect of the disorder that has a PD of 99.99 of being positive (median = 0.14, 89%CI[0.07,0.22]) and significant (0.09% in ROPE), such that AN had more false alarms (mean = 0.28, SD = 0.12) than controls (mean = 0.11, SD = 0.11).

Concerning the RT at the Stroop there is no evidence (BF = 0.59) of an effect of the groups, similarly there is weak evidence (BF = 1.26) of an effect of the group for correct recall face proportions at the RBMT-3.

Table 1 Summary of the demographics and clinical data.

	Descriptive Statistics		Posterior distribution				
	AN	Control	Median	89% CI	PD%	ROPE%	BF
Age	30.00 (10.46)	25.08 (1.78)	3.81	0.60,7.09	96	0**	2.45
Education	13.22 (0.67)	17 (1.00)	-3.71	-4.27,3.0	100*	0**	6.24e+8***
BMI	15.95 (1.96)	21.89 (2.83)	-5.55	-7.33,3.81	100*	0**	6.01e+3***
DT	12.89 (10.61)	5.40 (6.49)	6.07	1.01,10.53	97.5*	0**	3.25***
B	3.00 (4.00)	3.52 (3.98)	-0.36	-2.57,1.67	60	0.06**	0.37
BD	22.00 (10.21)	13.08 (8.43)	7.15	1.16,12.87	98*	0**	3.75***
EDRC	37.89 (22.33)	22.00 (15.19)	12.75	2.52,23.92	97.8*	0**	2.65

AN, anorexia nervosa; B, bulimia; BD, body dissatisfaction; BF, Bayes factor; CI, credible interval; DT, drive for thinness; EDRC, eating disorder risk composite; PD probability direction; ROPE, region of practical equivalence

* Clear direction effect

** Significant ROPE

*** BF with moderate to decisive evidence

5.2. SiFI Task Performances

Bayesian t-tests were used to compare results between the groups. Within-analyses are reported elsewhere (Chirico et al., 2019). For the accuracy proportions of the SiFI measure, we found decisive evidence (BF = 1.52e+5), in favor of the presence of a negative (median = -0.64, 89%CI[0.80,0.48]) effect of pathology with a PD of 100% that is significant (0% in ROPE). AN group showed lower accuracy (mean = 0.01, SD = 0.02) compared to controls (mean = 0.68, SD = 0.28). Unimodal visual performance was also higher in healthy females (mean = 0.84, SD = 0.14) than in AN patients (mean = 0.25, SD = 0.16). In favor of this evidence, we found a decisive BF of 5.96e+8, in favor of an effect of 100% (PD) of being negative (median = -0.57, 89%CI[-0.67,0.48]) and that is considered significant (0% in ROPE). Again, we found decisive evidence (BF = 1.32e+20) of an effect of group (100% PD) of being negative (median = -0.83, 89%CI[0-.88,-0.77]) and significant (0% in ROPE). In this sense, AN showed lower accuracy (mean = 0.11, SD = 0.12) compared to controls (mean = 0.94, SD = 0.06) for bimodal stimuli. Finally, auditory discrimination accuracy was also higher in controls (mean = 0.95, SD = 0.16) than in AN individuals (mean = 0,

SD = 0). Concerning this we found decisive evidence ($BF = 3.15e+14$) of a negative effect (median = -0.93, 89%CI[-1.03,-0.84]) with a PD of 100% and an group effect that is considered significant (0% in ROPE)

5.3. EMR Task Performances

First, we checked if sound had an effect on EMR, there was no effect of the sound on recall performances in the two groups, therefore we computed total proportions for images with and without sounds. We found an interaction effect (group x R/K/N answers), in particular a moderate evidence ($BF = 19.74$), in favor of the interaction group by N responses with an effect (100% PD) that is negative (median = -0.19, 89%CI[-0.28,-0.10]) and significant (0% in ROPE). In this way, AN patients showed less forgetting (mean = 0.36, SD = 0.18) than controls (mean = 0.56, SD = 0.16). We found also a significant (0% ROPE) PD (97%) positive tendency for R responses (median = 0.10, 89%CI[0.01,0.19]) in favor of the AN group, however evidence was very low for this ($BF = 0.42$). In order to analyze R false memories in the groups, we run a Bayesian t-test. We found a moderate evidence ($BF = 22.42$), in favor of a group effect (99.7% PD) that is positive (median = 0.13, 89%CI[0.05,0.20]) and significant (0.2% in ROPE). In this sense when they were asked to describe R memories, AN had more proportions (Figure 1) of false memories (mean = 0.18, SD = 0.23) than the control group (mean = 0.02, SD = 0.03).

Figure 1 R false memory assessed with the EMR task

5.4. Results and Feasibility of ML Classification

Training performances of k-NN and SVM radial models resulted from the 10-fold CV repeated 5 times in the two sets of resampled (fit1, fit2) training datasets are displayed in Figure 2. Best tune for the k-NN models was $k = 6$ and for the SVM radial $C = 1$ and 2 (first and second model respectively) a $\sigma = 0.04$ for both. Mean accuracy for the two train sets was 0.96 with a mean Kappa of 0.83 for the 6-NN and mean accuracy of 0.98 and mean Kappa of 0.93 for the SVM radial. Mean scaled values resulted from the two models for each algorithm for variable importance were computed for all the predictors; any differences resulted in the two group (see Figure 3 for fit1 and 2 aggregated variable importance of SVM radial). ROCs and area under the curve (AUC) were computed. AUC was 0.99 for both groups, models and algorithms. Figure 4 shows ROC, sensitivity and specificity for the two models tested on both algorithms. ROC curve for 6-NN and SVM radial are shown in Supplementary material Figure 5 and 6, predictors transformation distribution in Figure 7 and parameters tuning in figure 8, 9, 10, 11. As accuracy performances were equal in both models of the algorithms, we calculated the confusion matrices for the first set splits (fit1) with the 6-NN and SVM radial models. Table 2 shows performances of the models.

Figure 3 Training performances of the two (fit1, fit2) resampled datasets tested with the two algorithms (svm, knn); svm = support vector machine radial; knn = 6-nearest neighbors.

Figure 2 Variable importance for the SVM radial SVM, support vector machine; SiFI, sound-induced flash illusion; BMI, body mass index; rt_Stroop, reaction time at the Stroop test; RBMT_FAp, Rivermead behavioral memory test false alarms proportions; RBMT_p, Rivermead behavioral memory test correct proportions; Np_tot, forgetting proportions; Kp_source, source memory for know responses; BD, body dissatisfaction; DT, drive for thinness; R_false, false memory for remember responses; err_Stroop, errors at the Stroop test; Rp_tot, remember proportions; B, bulimia; Rp_source, source memory for remember responses; Kp_tot, know proportions.

Figure 4 Specificity, sensitivity and ROC of the tested algorithms for the two resampled dataset (fit1,fit2); ROC, receiver operating characteristic; svm, support vector machine radial; knn, 6-nearest neighbor.

Table 2 Confusion matrices for the two algorithms for the first resampled dataset (fit1)

	6-NN		SVM radial	
Accuracy (95% CI)	0.92 (0.63,0.99)		1 (0.75,1)	
Balanced accuracy	0.83		1	
Sensitivity	0.66		1	
Specificity	1		1	
PPV	1		1	
NPV	0.90		1	
Prevalence	0.23		0.23	
Detection rate	0.15		0.23	
	Actual			
Predicted	AN	control	AN	control
AN	2	0	3	0
control	1	10	0	10

AN, anorexia nervosa; CI, confidence interval; NN, nearest neighbor; NPV, negative predictive value; PPV, positive predictive value; SVM, support vector machine

6. Discussion

In this proof-of-concept study, we explored performances in AN and healthy individuals on a set of crucial neurocognitive measures and their relative impact for discriminating the two groups. We found that: 1) AN group showed impaired MSI, unimodal (visual and auditory) and bimodal accuracy compared to healthy participants; 2) AN individuals showed greater proportions of false R memories compared to control group, this last aspect is also confirmed within the domain of memory with higher number false alarms at the RBMT-3; 3) AN individuals had less inhibitory control compared to healthy females; 4) the whole set of predictors showed good variable importance but particularly, MSI and unimodal measures are more relevant for diagnostic classification ML (AN vs. control) than BID gold-standard questionnaire subscales.

By a neuroscientific point of view, AN is a psychiatric disorder that is characterized by alterations in sensory and cognitive domains (Gaudio, Brooks, & Riva, 2014). Sensory deficits consist of unimodal but also MSI processing (Riva & Dakanalis, 2018). Indeed, we found in the SiFI task that AN individuals have impaired discrimination abilities for unimodal (visual and auditory) and bimodal stimuli but also lower MSI ability. Compared to healthy controls, AN subjects showed altered visual, auditory and bimodal perceptual abilities; in this sense unimodal and bimodal audiovisual stimuli are bond together instead of being perceived as distinct percepts. This might explain previous altered perceptual abilities in AN, such as vision (Cornelissen, McCarty, Cornelissen, & Tovee, 2017; Engel & Keizer, 2017a). Visual stimuli are particularly relevant for the experience of the body (Engel & Keizer, 2017a; Zopf et al., 2016) but in our study we found that this deficit might encompasses another sensory domain (audio stimuli) and their correct integration. However very few has been done to investigate impairment in auditory processing (Chirico et al., 2019; Goldzak-Kunik, Friedman, Spitz, Sandler, & Leshem, 2012). More, to our knowledge, no studies (except our pilot by (Chirico et al., 2019) on AN investigated cross-modal enhancement (Gingras, Rowland, & Stein, 2009) (i.e., visual + auditory stimuli), which was found to be reduced compared to controls. These findings are also in line with Chirico and colleagues (Chirico et al., 2019) findings on unimodal and bimodal stimuli in AN. Moreover, we found impaired MSI and temporal binding window in our AN group compared to HCs. This is in line with previous research on altered MSI processing in this disorder (Eshkevari et al., 2012, 2014; Keizer et al., 2012; Riva & Dakanalis, 2018); further altered temporal processing of multisensory stimuli can be due to altered multisensory prefrontal cortex neurons (Romanski & Hwang, 2012), which might be related to the so-called “*multisensory executive functioning*” (Hunt & Kingstone, 2004). Jointly, in spite of normal EM we found that in some recollections AN memory is distorted as confirmed by higher proportions of false memories at the EMR task and at the RBMT-3. These

findings tap different aspects of memory: one mainly related to a recollection experience provided by a partial visual cue, the other to a false recognition of complete visual information. This pattern of impaired memory is consistent with previous memory research in AN (Malighetti et al., 2016; Nandrino et al., 2006; Riva, 2012; Serino et al., 2015; Weider et al., 2015). By a phenomenological point of view, disrupted recollection or recognition of visual stimuli might affect episodic memories related to critical factors such as body, food, relational episodes (Daggleish et al., 2003; Hermans, Pieters, & Eelen, 1998) and to the subjective sense of self (Prebble, Addis, & Tippet, 2013). Further, we found that AN individuals tend to forget less material; however, when participants of the AN group were asked to justify R responses part of these responses were distorted. Hence, instead of responding N when they saw the visual cue, they thought they remembered the scene from the detail but in true the episode was inaccurately imagined and described. Further, we found higher error at the Stroop task in the AN group that shows higher impulsivity. On the one hand, this might explain the processes reported above of the N-to-R false memory responses in AN, where altered hippocampus and prefrontal cortex and reduced recollection and executive functioning (e.g., inhibition) play a critical role in the creation of false memories (Devitt & Schacter, 2016; Lövdén, 2003); on the other hand, this could be related to a broader executive function problem in AN (Gillberg et al., 2010). Indeed, frontal deficits are known in AN individuals and executive functions could impact on both perceptual and memory functions (Heled et al., 2014).

These findings are confirmed by machine learning analysis that shows that using objective neurocognitive and self-reported psychological variables allow to discriminate with high accuracy the two groups. In particular, sensory, memory and executive functions predictors have greater impact than the eating disorder subscales of the EDI-3 for computing the classification. Using behavioral markers in psychiatric diagnosis and nosology is one of the aims of the Research Domain Criteria (RDoC) of the National Institute of Mental Health (Cuthbert, 2015). Indeed, RDoC proposes an innovative diagnostic classification that tries to overcome limitations of DSM-5 and ICD-11 manuals based on classic clinical psychiatric investigation. RDoC has the objective to find a wide range of genetic, neurobiological, cognitive and psychological markers for better mental disorders diagnosis and treatment.

Further, these bodily and neurocognitive factors have great relevance within the account of predictive coding. Indeed, executive functions, attention, memory and unimodal abilities can impact MSI processing in a bottom-up and top-down fashion (Alexander & Brown, 2018; Dijkstra, Zeidman, Ondobaka, van Gerven, & Friston, 2017; Gordon, Tsuchiya, Koenig-Robert, & Hohwy, 2019; Picard & Friston, 2014; Riva & Dakanalis, 2018; Talsma, 2015). According to the ALT (Riva

& Dakanalis, 2018), predictive coding is a critical element in the construction of body-related memories, which cannot be updated with current sensory information coming from the body. Despite positive results, our findings are preliminary and must be taken with caution. First, sample size of AN is small, therefore groups are unbalanced; hence, results and, particularly, ML classification should be taken as a feasibility study on the use of the selected predictors for further studies. Second, we only investigated the MSI of audiovisual stimuli, clinically relevant experiences can occur also in other sensory integration processes such as touch and vision and results cannot be generalized with what concerns these phenomena. Then, we considered neutral stimuli for the EMR task, possibly results might change when using arousing stimuli to be remembered, indeed autobiographical memories are always characterized by an emotional valence. However, as research in the field of MSI and episodic memory in AN is at its infancy, these findings could be a starting point for future researches. We suggest deepening other aspects of MSI in this population with other paradigms and stimuli potentially with immersive virtual reality. Again, behavioral task and immersive technologies could be used to assess episodic memory for emotional experiences (Repetto et al., 2019; Serino & Repetto, 2018).

Finally, the results can be applied to create and test innovative therapeutic solutions that can restore MSI and improve memory retrieval of individuals that suffer from AN. For instance, (Serino et al., 2016) and colleagues showed that with immersive virtual reality is possible to modify the body memory in AN. Again, the combined use of neuroscientific measures and innovative methods like ML can be useful for diagnosis and prognosis of this complex psychiatric disorder (Haynos et al., 2020; Lavagnino et al., 2018; Vaughn et al., 2019).

7. Conclusion

To the best of our knowledge this is one of the few existing studies exploring audio-visual integration and episodic memory in AN. Our findings showed deficits in MSI in terms of lower discrimination accuracy and also for both unimodal and bimodal stimuli, and deficits in episodic memory in terms of higher false memories and false alarms in episodic and visual recognition in AN subjects compared to HCs. MSI is a salient process for the construction of body self-awareness (Blanke, 2012), thus its alteration could be related to the disturbed experience of the body characterizing AN subjects. Furthermore, memory plays a crucial role in the construction of body representation (Riva, 2018). Our body image is constructed upon the integration between our (offline) memory of the body and the (online) perception of the body “here and now” (Dakanalis et al., 2016; Riva, 2014). Our findings are in line with ALT suggesting that BID in AN might reflect an alteration other neurocognitive measures such as MSI and memory (Riva, 2011; Riva, 2012;

Riva & Gaudio, 2018). Specifically, false memories found in this study could be read within the framework that explain AN as the result of a multisensory processing deficit in the way expected (using predictive coding) versus experienced (from perception) bodily experiences are integrated (Riva 2018). Alterations in episodic memory could affect the predictions made using the stored information about the body (Riva & Dakanalis, 2018) and thus their integration of sensory data arriving from real-time multiple sensory modalities and internal information. In this vision, MSI deficits represent a failure in this functional adaptation process, which may impair the emotional and bodily experience of the individual (Riva, 2012; Riva & Dakanalis, 2018; Riva & Gaudio, 2018). Finally, machine learning analysis confirmed the importance of our measures in the classification of AN and control subjects. MSI along with memory could be crucial factors for improving diagnosis and consequently design innovative therapeutic solutions that tap critical bodily and cognitive elements altered in AN with new technologies such as virtual reality.

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