The recognition of facial emotions in spinocerebellar ataxia patients

The recognition of facial emotions in Spinocerebellar Ataxia patients

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ABSTRACT

Background: Patients with cerebellar lesions present some affective and cognitive disorders, defining a peculiar pattern of cognitive impairment, so called "Cerebellar Cognitive Affective Syndrome". This pattern has been confirmed in many genotypes of Spinocerebellar ataxias (SCA), a group of genetically defined pathologies characterized by the degeneration of the cerebellum and its connections. Recently, in SCA patients, some authors focused the interest on social cognition evidencing an impairment of Theory of Mind and basic emotions recognition by verbal material. The recognition of emotions in faces is an essential component of social cognition therefore we assessed this ability in SCA patients, expanding the study from the basic verbal emotions to the basic and social visual emotions recognition.

Methods: We assessed facial emotions recognition using two basic and social emotions tasks in a group of SCA patients together with a complete clinical and neuropsychological evaluation. We compared results with the performance of a control group.

Results: We demonstrated a significant difference between patients and controls both in basic and social emotions recognition, although we found a specific impairment only for social emotions. The deficit was not correlated to clinical and demographic features. The cognitive and psychological profile did not explain the impairment in emotions recognition.

Conclusions: This result supports the hypothesis that the impairment in social emotions recognition could be specifically related to a defect in the cortico-cerebellar network.

INTRODUCTION

The ability to recognize emotions expressed by faces is essential for the functioning of human interactions. Traditionally, the recognition of identity and emotion in human faces involves distinct processes linked by an initial visual processing. This hypothesis is based on previous results of lesion neuropsychological studies [1], where patients showed a double dissociation or studies on diseases such as autism and prosopagnosia where one of the two abilities is relatively preserved while the other is compromised [2,3]. Recently it has been shown that this partition is only an oversimplified model, since neuroimaging studies showed that brain networks involved in both tasks have large areas of overlap and that familiarity and emotional valence modulate the activation and the behavioural performance [4]. In a recent interpretation, the visual analysis is therefore not separated from the affective analysis, having a similar and equally important role to that of memory in perceiving actively, generating predictions about the future and preparing the body for an appropriate action [5].

The vision of a face triggers off the activity of a distributed network composed of many cortical areas influencing each other with great complexity and with a relative dominance of the right hemisphere [5-7]. In this distributed network, different regions may be associated specifically with different skills, showing a degree of specialization that fits in with traditional theories. For example, different parts of the fusiform gyrus and superior temporal cortex may be specialized in recognition of invariant aspects (e.g. identity) or dynamic aspects (e.g. expressions).

A strong attentional and emotional modulation of the visual processing made from visual cortex has been demonstrated, involving distant but interconnected cortical areas. [8]. For attentional influence the main role is played by the fronto-parietal cortex, whereas in the emotional influence the amygdala, which has a recognized role in fear processing [9], is the principal actor. The role of amygdala in the emotional modulation of visual processing is supported by functional studies that demonstrated the great amygdala activation during the vision of negative facial emotional expressions, fear in particular. [10].

The ability to recognize emotions from facial expression is correlated to the affective Theory of Mind (ToM), the ability to attribute to others mental states, beliefs, intents, desires and the area of activation between this two components of social cognition overlap [11]. As it is known, the impairment of ToM represents one of the main psychological features of patients with autistic spectrum disorders, a group of developmental pathologies where many studies demonstrated a deficit in the recognition of facial emotions [12] and a different activation of cerebellum, mesolimbic and temporal cortical regions, during the processing of facial emotional expression compared with controls [13]. In these pathologies, characterized by aberrant emotional processing, some authors described the presence of cerebellar abnormalities and consequently a dysfunction of cerebellar-cortical network [14, 15].

It is still not clear how the cerebellum participates in emotional processing, but in a recent meta-analysis authors emphasized that cerebellum is active during the perception of emotional faces without difference across single basic emotions, in concert with the activation of many visual, cortical and limbic areas, suggesting a general role of cerebellum in emotional processing [16]. This role is also supported by the results of functional studies that demonstrating a cerebellar activation during the production of emotions by the observation of emotional visual stimuli [17] or during the implicit processing of facial emotions [18].

The Spinocerebellar ataxias (SCA) are a group of rare genetically defined diseases characterized by the degeneration of cerebellum and its cortico-cerebellar connections. In these pathologies many studies demonstrated the presence of a cognitive impairment [19-21] associated with various degrees of emotional and neuropsychiatric disorders [22, 23]. This peculiar cognitive profile has been defined by Schmahmann and collegues as “Cerebellar Cognitive Affective Syndrome” (CCAS) including frontal, attentional, visuospatial, memory, language impairment and various affective and personality alterations [24]. Recently, the interest in SCA has been focused on the presence of an impairment also of social cognition, a general concept comprising various psychological concepts from the perception of emotions to ToM, and particularly some authors

demonstrated that SCA 3 and 6 genotypes[25] have an impairment of ToM abilities, without deficits in the attribution of basic emotions evaluated by a verbal task, suggesting that cerebellum may be exclusively involved in this aspect of social cognition. However, more recently, the same authors demonstrated that SCA 1, 2 and 7 patients are impaired also in verbal emotions attribution task and consequently they suggested that social cognition impairment in Spinocerebellar ataxia patients is not homogeneous among the various genotypes [26].

Aim of the study

In this study we hypothesized that, being the cerebellum connected to several key areas of the network involved in the faces' analysis, through deep cerebellar nuclei and thalamus and being demonstrated that cerebellum participates also in the facial emotional processing, patients with spinocerebellar degeneration could also have an impairment in other important aspects of social cognition, as in the recognition of emotions by faces, where an impairment in ToM and verbal emotions attribution tasks has been found.

We tested for this hypothesis in a group of patients with Spinocerebellar Ataxias, of various genotypes, assessing their performance during two emotions recognition tasks, using both basic and social emotions, together with their neuropsychological and clinical evaluation, to see if the cognitive, psychological and clinical profile could influence the performance in emotional processing.

MATERIALS AND METHODS

Patients

Twenty SCA patients (13 males) belonging to different genotypes (9 SCA2, 5 SCA6, 2 SCA7, 4 SCA8), have been recruited from our Ataxia Center (Department of Neuroscience, AOU San Giovanni Battista, Turin, Italy). Twenty age, sex and education-matched healthy subjects have been enrolled as a control group. For all subjects we collected demographic (age, education) and clinical data (age at onset and duration of disease).

We submitted the experimental design to the Ethical Committee of the Department of Psychology for approval. Informed consent was obtained from all participants and the study was in line with the declaration of Helsinki. Patients and controls did not follow any pharmacological treatment at the time of the study.

Patients underwent to an accurate neurological examination using the International Ataxia Rating Scale (ICARS) [27] to assess the severity of ataxia symptoms. For all patients, we considered the ICARS oculomotion sub-score, as a measure of the nystagmus, saccadic pursuit and dysmetria of saccades, that are variably presents among various SCA genotypes.

An expert neuroradiologist examined the patients' brain MRI of patients, reporting an evaluation of the degree atrophy in the following areas: cerebral cortex, cerebellum and pons, by a 4-points qualitative scale (0 = absence of atrophy, 1 = mild atrophy, 2 = medium atrophy, 3 = severe atrophy).

Neuropsychological assessment

We assessed the recognition of basic emotions with the Ekman 60-Faces Test [28], where photographs of faces (50% females) displayed happiness, sadness, disgust, fear, surprise or anger and the Tamietto 50-Faces Test [29] for social emotions, where photographs (50% females) displayed flirtatiousness, admiration, arrogance, guilt or neutral expressions (see fig. S1 in Electronic Supplementary Materials, ESM). In both tests participants, after a training trial, were required to choose the label that best described the emotions displayed by each face, among the

number of 6 possible basic emotions and 5 social emotions, without time limits, to minimize the bias linked to the individual processing speed (see ESM for the complete instructions). For each task we recorded all the answers and the mistakes and then we calculated the number of correct responses and substitutions. Furthermore, we used a large battery of neuropsychological tests, comprehensive of all the domains involved in the CCAS, to evaluate the differences in patients' and controls' performance and to find a correlation between the cognitive performance and the results on face emotions recognition tasks.

The neuropsychological battery comprised the Mini Mental State Examination (MMSE) for general intellectual abilities [30], the Trail Making Test-B (TMTB) [31] and the Colour-Word (CW) interference of the Stroop Test [32] for attention, the Digit span Backward (Digit Span BW) for working memory, the Buschke Selective Reminding Test (BSRT) [33] for verbal learning in the Short term (STR), Long term (LTR) and Delayed recall (DR) memory, the Benton Visual Retention Test (BVRT) [34] for visual memory, the Tower of London test (ToL) [35] and the Wisconsin Card Sorting Test (WCST) [36] for executive functions, the Phonological (PHO) and Semantic (SEM) Fluency for language production [37], the Judgment of Line Orientation test (JLO) [38] for visuo-spatial perception. Finally, we evaluated the presence of depression and anxiety using two self-administered scales, respectively the Zung Self-Rating Depression Scale (SDS) [39] and the State-Trait Anxiety Inventory Y form (STAI-Y) [40].

Statistical analysis

We used the statistical package SPSS™ 13 for Windows (SPSS Inc., Chicago, USA) to analyze the data.

Groups' comparisons

Patients were compared with controls in respect to demographic and neuropsychological data using Mann-Whitney U, $p_{corr}<0.05$ on exact 2×1-tailed significativity corrected for multiple comparison was considered as significant. We used the step-down Finner formula for the correction:

$p_{corr} = 1-(1-p_i)^{\frac{n}{i}}$, where *i* is the ith smallest p-value in the list and *n* is the number of considered comparisons [41,42].

Patients were divided in two subgroups on the basis of the structures specifically degenerating in each condition. The first subgroup (Olivo-Ponto-Cerebellar Atrophy group, OPCA) comprised 11 patients (9 males) carrying genotypes associated with cerebellar and brainstem degeneration (SCA2 and SCA7). The second subgroup (Olivo-Cerebellar Atrophy subgroup, CA) comprised 9 patients (4 males) carrying genotypes associated with a relatively "pure" cerebellar degeneration (SCA6 and SCA8). We compared the demographic, clinical and neuropsychological data of the two subgroups using again Mann-Whitney U ($p_{corr}<0.05$). We also compared the two subgroups with two controls (A and B) subgroups matched (sex, age and education) with OPCA and CA subgroups.

We created more subgroups to untangle the possible effect of mood. So we compared with Mann-Whitney U ($p_{corr}<0.05$) the SCA patients with (11 patients, 6 males, SDS $\geq$ 50) and without depression (9 patients, 7 males, SDS < 50).

Correlations

We used Kendall's Tau-b to calculate the rank correlations between Tamietto, Ekmann and clinical-demographic variables. We made 50 correlations afterwards, to correct for multiple comparison, we used the FDR Benjamini-Hochberg-Yekutieli correction [43], setting the rating of false positive to less then 5%, $q \leq 0.05$, find *k* that $p(k) \leq \frac{k}{50}(qp)$, in our sample $p(k) \leq 0.0047$. We calculated the significant correlations in the total SCA sample, OPCA and CA subgroups.

ANCOVA

We used two ANCOVA models to look if the group factor (SCA vs. controls) could explain the differences between emotions recognition (Ekman or Tamietto). We included the age, education and depression as nuisance covariates. The equations of the models were: $Y = \beta_0 + \mu_j + \beta_1 \cdot Age + \beta_2 \cdot Edu + \beta_3 \cdot Dep + \varepsilon$, where *Y* stands for Ekman or Tamietto scores, μ_j

is the group factor, *Age* are how old were the subjects, *Edu* are the years of school attended, *Dep* is the SDS Zung scores and ε is an error term.

We used F tests (see ESM) to look if some of the reduced models (3 models with only two covariates, 3 models with only one covariate) nested in the previous full models could explain more parsimoniously the data. When we found the best models, again, we used ANCOVA to look at the group factor significance.

We repeated the ANCOVA analysis with the best choice models for Ekman and for Tamietto adding an ICARS oculomotion score covariate to look if this parameter could be influential. To simply study a possibly moderator effect of oculomotion we also introduced in the equation the terms of interaction between oculomotion and the other covariates. We also compared these new more complex models with the old ones with F tests.

Recognition Matrix

We created square matrices X_r^c containing as many rows and columns as emotions [44] for Ekman and Tamietto, separately. The rows represented the faces presented to the participants, and were ordered by similarity as perceived by normal subjects [44, 45], adjacent emotions are judged to be more similar, from the first to the last row: happiness, surprise, fear, anger, disgust, sadness for Ekmann; flirtatiousness, admiration, neutral, guilt, arrogance for Tamietto. The columns represented how the stimuli were verbally recognized. The columns were ordered in the same way of the rows, so that correct identifications are on the diagonal of the matrix and wrong identifications are in the elements external to the diagonal of the matrix. We plotted the recognition matrixes associating a colour scale to the percent of answers in every category [45].

We decomposed the matrices X_r^c in a symmetric (off diagonal elements symmetric respect to the diagonal are equal, i.e. $x_a^b = x_b^a$) and antisymmetric part ($x_a^b = -x_b^a$) with the formula: $X = S + A = \frac{1}{2}\left(X + X^t\right) + \frac{1}{2}\left(X - X^t\right)$, where the symmetric part *S* come from the half of *X* added to its transpose and the antysimmetric part *A* from the subtraction. We interpreted *S* as a measure of

the ability to distinguish between emotions and *A* as the tendency to have some bias in the recognition task towards a particular direction (a positive or negative emotions recognition bias for example could be uncovered with this technique). See the ESM for a more detailed explanation and an example of *X*, *S* and *A*.

Logistic Regression

We used a binary logistic regression with the group membership (SCA or control) as dependent variable. We used both the Forward Likehood Ratio (LR) and Backward LR stepwise methods with two set of variables as independent (first set demographic+emotions: age, education, depression, Ekmann, Tamietto; second set demographic+emotions+cognition: age, education, depression, Ekmann, Tamietto, CW Stroop) to select the best combination of variables capable to predict the membership of a participant. We selected the Stroop CW as representative of cognitive impairment because it was the test most frequently impaired in the patients population.

RESULTS

Demographic and clinical data of patients and controls are represented in tab.1. Patients and controls were age and education-matched (p=0.97 and p=0.16 respectively). Also OPCA and CA subgroups were age and education-matched (p=0.11 and p=0.30 respectively) although they differed for disease duration, that is longer for CA (p=0.01).

Neuropsychological profile

In tab.2 and tab. S1 the results of the neuropsychological tests in SCA patients, OPCA, CA subgroups and controls are reported.

The neuropsychological evaluation of SCA revealed in most of patients (65%) an impairment in selective attention and resistance to interference (Stroop), almost in a half (55%) in executive functions (WCST categories) and the presence of depression of mood (ZUNG). From 15 to 30% of patients have an impairment in visuo-spatial organization (JLO), sustained and shifting attention (TMT-B), visual short-term memory (BVRT), working memory (DIGIT Span BW), motor executive planning (TOL), phonological fluency (PHO) and anxiety (STAI-Y1 and 2).

Only 5% of patients had a MMSE under the cut-off whereas nobody presented long-term, delayed verbal memory (BSRT LTR and DR) or semantic fluency (SEM) impairment.

As shown in tab.2 patients and controls significantly differed for general intellectual abilities (MMSE $p<0.01$), attention (TMT-B p=0.02; Stroop CW $p<0.01$), long-term and delayed verbal memory (BSRT $p<0.01$), visual short-term memory (BVRT $p<0.01$), motor executive planning (TOL p=0.01), executive functions (WCST p=0.03) and phonemical fluency (PHO fluency p=0.02). They did not differ for depression and anxiety. We did not find any significant difference between OPCA and CA subgroups except for depression that was more present in CA patients (tab. 1) and pons atrophy that was more present in OPCA (tab. 1).

Emotions recognition tasks

Results of basic and social emotions recognition are reported in tab. 3.

Patients and controls were both above the cut-off in the basic emotion recognition task although the performance was significantly different in patients compared to controls in the total number of correct responses and in the recognition of *sadness* (looking at every single emotion). Controls had a over the cut-off performance in the Tamietto task, whereas patients had a under the cut-off performance in all emotions recognition. Patients and controls significantly differed in the total number of correct responses and in the recognition of both the *positive* and *negative* emotions (considering the valence). Looking at every single emotion, the greater difference is for *flirtatiousness* followed by *guilt*. We did not find any performance difference in the two emotion tasks between OPCA and CA patients.

The ANCOVA analysis demonstrated a significance difference between SCA and controls both in Ekman task and in Tamietto tasks (see ESM for a complete report). In the full model for Ekman (r^2=0.49, p<0.01) we found a constant term of 34, a group factor of 4 (p=0.02), β coefficients of -0.2 for *Age* (p=0.03), 0.7 for *Edu* (p=0.01) and 0.2 for *Dep* (p=0.03). The final selected model for Ekman (r^2=0.39, p<0.01) had a constant term of 59, a group factor of 6 (p<0.01), β coefficient of -0.3 for *Age* (p<0.01).

In the full model for Tamietto (r^2=0.54, p<0.01) we found a constant term of 10, a group factor of 5 (p=0.02), β coefficients of -0.03 for *Age* (p=0.30), 1.1 for *Edu* (p<0.01) and 0.01 for *Dep* (p=0.07). In the first reduction step only no *Age* and no *Dep* models met the F test (F_{crit}=4.12, no *Age* F=0.09, no *Edu* F=12.78, no *Dep* F=0.02), but we chose to remove depression for the greater r^2 of this reduced model (no *Age* r^2=0.52, no *Dep* r^2=0.54). The final selected model for Tamietto (r^2=0.54, p<0.01) had a constant term of 12, a group factor of 5 (p<0.01), β coefficient of 1.0 for *Edu* (p<0.01).

Effect of clinical, demographic and psychological variables

To explain the effect of clinical and psychological variables on test performance, we divided patients in two subgroups depending on the presence of depression (Depressed and Euthymic). We calculated the difference in the performance on neuropsychological and emotions recognition tests.

Depressed and Euthymic patients differed for age, education and disease duration (depressed patients are less educated and have a longer duration of disease, see tab. S2). The two subgroups differed in the performance in some neuropsychological tests (attention, semantic fluency, working memory, see tab. S2) but they did not differ in the performance in the two emotions recognition tasks (tab. S2).

The correlations between other clinical features (ICARS total score and sub-scores, see tab. S3 in ESM) failed to demonstrate a direct association of these variables with the performance of the emotions tasks. To study oculomotion we added to the models of the previous section the ICARS oculomotion covariate and its interaction term with the other covariates. Both for Ekman and Tamietto this models met the F test (F_{crit}=3.27, Ekman no interaction F=0.47, Tamietto no interaction F=2.45) and again we preferred the previous reduced models, and the interaction terms were also not significant in both cases (Ekman p=0.36, Tamietto p=0.11).

Correlations between neuropsycological profile and emotions tasks

In tab. 4 the correlations, correct for multiple comparison, between the emotions recognition tests results, the neuropsychological profile and the clinical and demographic features of SCA, OPCA and CA patients are represented (see tab. S3 in ESM for the all the correlations). The cognitive profile (in particular attention, verbal memory and semantic fluency) significantly correlates with the recognition of basic emotions in the SCA group, attention and visual memory in OPCA group and semantic fluency in CA and also with the Tamietto task for a few tests, however these correlations, corrected for multiple comparison, survive only for Ekman task.

We found a significant correlation between the Ekman and Tamietto tasks (r=0.48, sig. FDR corrected).

Answers distribution in patients and controls

In tab. S4 in ESM emotions mismatched for patients and controls are shown.

The maximum of false recognition is only in patients for *admiration* and *neutral* emotions in Tamietto test and in both patients and controls for *surprise* in Ekman test.

The fig. 1 shows the distribution of answers in patients and controls in Ekman and Tamietto task. In fig. S2 in ESM, the symmetric and asymmetric part of the matrix for basic emotions revealed an almost identical pattern of confusing bias as of interpretational bias. Conversely, as shown in fig. S3 in ESM, in social emotions recognition task patients have a more widespread pattern of confusing bias and a tendency to interpret as neutrals the emotional expressions.

SCA characterization

The logistic binary regression gave the same results, selecting the same model, for both the Forward LR and the backward LR methods. For the demographic+emotions set we obtained a 74% (70% for controls, 78% for SCA) of correct classifications with the final model: $Y = \frac{1}{1+e^{-Z}}$; $Z = a + b \cdot TAM$, where a=3.32, b=-0.14 (odds ratio = 0.87, Wald p=0.01) and *TAM* is the Tamietto score. The model had a -2 Log Likehood = 44, a Hosmer-Lemoshow test = 0.45 and a Nagelkerke r^2=0.27. If we considered also the cognitive variable (Stroop CW) the final model (82% correct classifications, 90% for controls, 72% for SCA) was: $Y = \frac{1}{1+e^{-Z}}$; $Z = a + b \cdot TAM + c \cdot CW$, where a=-0.47, b=-0.14 (odds ratio = 0.87, Wald p=0.04), c=0.002 (odds ratio = 1.02, Wald p=0.01). The model had a -2 Log Likehood = 32, a Hosmer-Lemoshow test = 0.69 and a Nagelkerke r^2=0.55.

DISCUSSION

The cognitive profile of our patients is homogeneous, in line with previous studies, with only 5% of patients having a MMSE score under the cut-off, supporting the knowledge that dementia is not a common feature of SCA patients, especially at an early stage of disease, a clear patter of dementia having been described only in SCA2 from 15% to 25% of patients [19,47]. This neuropsychological pattern is in accordance with the CCAS described by Schmahmann [24], combining executive, attentive and mild visuo-constructive impairment. We noticed depression in most of patients probably linked with the awareness of the disease's worsening [46]. Indeed OPCA and CA groups did not differ for neuropsychological performance, as reported in previously [47] but only for depression, more present in CA patients, more aged and with a longer duration of disease.

Patients had a relatively good performance in recognition of basic emotions, although they have more difficulty in respect to controls in recognition of *negative* emotions, on the contrary SCA patients have a severe deficit in the identification of social emotions, where we noticed a significant difference between patients and controls in the recognition of all emotions, both *positive* and *negative*.

Also the type of errors is similar in patients and controls in Ekman test (in fig. 1 we can observe an almost identical distribution albeit a slightly worse recognition in patients) whereas a clear difference exists in the social emotions task, where patients gave lots of random answers compared with controls. Patients and controls have the same pattern of confusing bias as of interpretational bias in basic emotions task. Conversely, in social emotions task patients have a more widespread pattern of confusing bias and a tendency to interpret as neutral the stimuli that they cannot clearly classify. Therefore, the more noteworthy result is the big difference between the performances in the two emotional tasks, and this result became more relevant observing that a correlation between the two tasks exists ($r=0.48$), the two tests sharing some common features, particularly they consisted of a forced choice of semantic labels, despite the different type of emotions displayed. The logistic regression supported the fact that the ability to recognize social emotions is a peculiar

feature that discriminates subjects with cerebellar atrophy and healthy subjects, beyond their cognitive abilities. The difference in recognition of basic and social emotions could be explained by the knowledge that basic emotions are easier to recognize, because they are innate and biologically universal to all humans. Social emotions, instead, are correlated to social background and their meanings are learned during development [44]. In SCA it is not known when the degenerative process starts but it is likely that degeneration of the cortico-cerebellar networks begins before the onset of motor symptoms, and that the cognitive and emotional skills and motor impairment had different time evolution in these pathologies [48]. On the other hand, the role of cerebellum in different forms of associative learning is well documented in animals in motor, emotional and cognitive tasks, so it is reasonable that it contributes to more complex associative learning processes also in humans [49]. From this point of view, cerebellum, more involved during the execution of complex tasks that have to be learned (as could be the recognition of social emotions educated during the socialization) it is probably not as crucial during basic emotions recognition.

Both social and basic emotions use a predictive / associative mechanism [5] to link the valence of stimuli observed to the possible consequences of a behaviour, but there are important differences. First, basic emotions are linked to autonomic functions, are innate and simple and not require comprehension of complex interpersonal dynamics (including the world representation observed from the other's perspective). Second, in case of social emotions, there is certainly a much more complex associative mechanism, that includes an interactive mutual exchange of signals between at least two subjects instead of a simple observation. The social emotions visual-motor patterns are not universal and innate; they must be learned and become automatic with a long learning process. Third, a social stimulus is more difficult to disambiguate presenting static images and requires a richer imaginative process.

Regarding the first point: we can refer, as theoretical framework, to the ToM and we can interpret the largest impairment of social emotions recognition as a selective impairment of this cognitive ability most needed for social stimuli. This hypothesis is consistent with the specific deficit in ToM

skills reported in SCA3 and SCA6 patients from Garrard et al. [25]. The network involved in ToM contains the superior temporal sulcus, the temporo-parietal junction and the ventral medial prefrontal cortex. A malfunctioning of the frontal node of the network, due to a specific fronto-cerebellar circuit reverberation [50], could be the neural substrate of the deficit observed.

The theory of control systems could explain the second point, assuming that an efficient planning and action execution requires two types of internal models: a Forward Model predicting the sensory consequences of a motor command (i.e. what the intended action should feel, look and sound like) and an Inverse Models that transform a sensory desired end-state (e.g. feeling, mental pictures and sounds) into a suitable motor command [51]. We could interpret the impairment found in our patients as a problem in storage and retrieval of the Inverse Models contained in the cerebellum, that, after training, allows people to associate the static and dynamic characteristics of one stimulus with the correct attribution of motor intentionality, and consequently, the more complex is the stimulus the greater the loss of efficiency is.

Moreover, it is possible that the effort amount needed to give meaning to social stimuli is much bigger and requires a constructive and imaginative load much more costly than for stimuli presented in a very poor way or far from the prototypical presentation in ecological context. Nomura et al. [52] focused on the ambiguously emotions expressed as representative of complex social stimuli. They showed that the main effect of ambiguity involved the anterior cingulated cortex, the dorsal part of medial frontal gyrus and the left inferior frontal gyrus in the general faces processing. Again a specific impairment of a reverberating fronto-cerebellar [50] loop might be the cause of our patient's deficit.

As we cannot exclude any of these hypotheses (and they are not mutually exclusive) we can think that all of these aspects may have a role in these pathologies.

The group of patients is of course heterogeneous, putting together different genotypes with different areas of degeneration involved. Indeed, the degenerative process in SCA2 and SCA7 patients also involves many pontine nuclei and it is variably associated with the degeneration of other structures

such as globus pallidus, subthalamic nucleus, red nucleus and cerebral cortex [53]. Conversely, in SCA6 and SCA8 the degeneration is almost confined to cerebellum, therefore these genotypes are better models of "pure" cerebellar degeneration [54]. On this basis, we divided patients in two groups (CA and OPCA) comparing their performances. The lack of any significant difference between the two groups supports the role of cerebellum in facial emotions processing. Moreover, in our patients, the deficit in emotions recognition could have also been related to their attentional or executive impairment and the correlation analysis showed that the cognitive profile could influence the performance on both basic and social emotions recognition tasks. Anyway the correlations between the neuropsychological profile and the social emotions recognition task do not survive to the multiple comparison analysis. This result strengthens the hypothesis of a more determinant role of cerebellum in social emotions recognition. As it is known, depression presence could be determinant for the onset of a cognitive decline and many studies demonstrated that patients with major depression have an impairment in the ability to recognize emotions by face [55]. In our patients, although depression degree is similar to that of controls, to exclude the influence of mood in performance, we divided patients in two subgroups on the basis of the presence or absence of depression, confirming that mood only partially influences attention, executive functions, verbal memory and semantic fluency, but does not influence the performance on the two emotions tasks.

We found that also clinical features did not influence the results, particularly the presence of eye movement's abnormality that could affect the correct faces perception. We think indeed that oculomotor impairment could play some role in a task where the exploration of space is important, but we also believe that absence of time limits in the tasks may dampen the effect so much not to appear in our data.

For SCA7, that notably has, intrinsically in the phenotype, a reduction of visual acuity linked to their macular degeneration, we noticed that our patients despite their visual defects, they performed well in other visual tasks of the neuropsychological battery: the Judgment of Line Orientation and

the Stroop Word Reading, This fact authorized us to consider valid their performances in the emotions recognition tasks and to include them in the sample.

The correlation between emotions recognition and clinical and demographic variables, failed to reveal any significant correlation (see tab. S3 and S4 in ESM), supporting the fact that an emotional processing impairment could exist also in patients with short disease duration and with mild ataxia, as part of the disease, closely related to degeneration of a cortico-cerebellar network.

A weakness of the approach of multiple comparison procedure in undersized groups is the lack of statistical power. We used "integrated power" (the average power over all possible values of alpha therefore, it depends only from sample size and size effect [56]) to simulate the chance that we will correctly distinguish the null and non-null studies (the lowest possible integrated power is 0.5, equal to chance, opposite to an integrated power of 0.95 that could be an optimal target) in respect to an hypothetical known Cohen's effect size d [57]. In our simulation with two groups of equal sample size of 10 the integrated power is 0.55 with a small size effect d=0.2, 0.66 with a medium size effect d=0.4 and 0.88 with a large size effect d=0.7. Apparently when we had negative results in our groups comparisons we could exclude only great effects. So we could not be totally sure that pons atrophy (OPCA vs. CA) or depression (Depressed vs. Euthimic) played a role in the emotions recognition, but the good matching (sex, age, education, depression) between SCA and controls (see tab. 1) and the important cerebellar atrophy shared by two subtypes of SCA (see tab. 1) mitigates the impact of this limitation on our conclusions.

In our study we decided to use de-contextualized expressions that in our opinion were necessary for our goals. Certainly the context in which a stimulus is embedded is a major determinant of recognition performance [58]. For example, 60-75% of the time, people "see" facial expressions intended to communicate fear as enraged when the images are embedded in contexts typically associated with anger [59-61]. Furthermore, reaction times and accuracy in the recognition of a facial expression displaying fear or happiness are modulated by the presence of another congruent or incongruent facial or bodily expression in the visual scene [62-63]. These effects indicate that

context is a potent factor that modulates recognition of basic emotions also. Aside from the emotion dimension, there is an extensive literature on object recognition showing that an object is more easily recognized when it is embedded in the context where it is typically encountered in everyday life [64]. To our knowledge, no prior study investigated in healthy population or in patients the effect of context in the recognition of social emotions, but it seems reasonable to assume that also in this case the context plays a prominent role in modulating performance. The study of context influence in the recognition of social emotions is certainly an important new avenue of research, but it was outside the aims of the present study and requires the preceding knowledge, not yet available, about recognition of de-contextualized social emotions.

Conclusions

The impairment finding in facial emotions recognition, in patients with Spinocerebellar Ataxia, expands the role of cerebellum in emotional processing; the prominent impairment in social emotions points to an important contribution of cortico-cerebellar network to more complex or social emotions recognition task.

We can think of several plausible assumptions behind what we observed. In SCA patients, a widespread damage to the cerebello-cortical loops could be present, which is easier to compensate in case of basic emotions, because of the robustness of phylogenetically oldest and wired redundantly neural circuits, or because of a gradient of difficulty resulting in higher load of circuits in case of social emotions.

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TABLES

Tab. 1. Demographic and clinical data of patients and controls

	Controls	SCA	p*	OPCA	CA	p**
Number/Male	20/13	20/13	-	11/9	9/4	-
Age [y]	54 (24)	53 (21)	0.97	49 (27)	66 (17)	0.11
Education [y]	9 (9)	8 (7)	0.16	8 (7)	6 (8)	0.30
Age at onset [y]	-	34 (16)	-	33 (18)	39 (17)	0.97
Disease duration [y]	-	16 (10)	-	15 (4)	24 (22)	**0.01**
ICARS score	-	46 (27)	-	46 (24)	45 (27)	0.84
ICARS oculomotion	-	3 (1)	-	3 (1)	4 (2)	0.05
Cerebral Cortex atrophy	-	0 (0)	-	0 (0)	0 (0)	0.77
Cerebellum atrophy	-	2 (0)	-	2 (0)	2 (1)	0.07
Pons atrophy	-	1 (2)	-	2 (2)	0 (0)	**<0.01**

Median (IQR), p = Mann-Whitney U significativity, in bold if p_{corr}<0.05 Finner step-down.
Aatrophy range: 0-3, 0 = no atrophy, 3= severe atrophy.
p comparison Controls-SCA, p** comparison OPCA-CA*

Tab. 2. Neuropsychological data of patients and controls

TEST		Cut-Off	Controls	%	SCA	%	p*	OPCA	CA	p**
MMSE		23.8	28.9 (0.9)	0	26.2 (1.9)	5	**<0.01**	27.1 (2.6)	26.2 (1.2)	0.39
TMT B		283	152 (89)	0	182 (93)	15	**0.02**	157 (154)	197 (77)	0.22
STROOP CW		172	124 (20)	10	207 (168)	65	**<0.01**	206 (68)	248(242)	0.80
DIGIT BW		3.5	4.0 (1.0)	10	4.0 (1.5)	20	0.16	4.0 (2.0)	3.0 (2.5)	0.80
BSTR	LTR	36	139 (29)	0	94 (78)	0	**<0.01**	113 (91)	83 (67)	0.93
	DR	2	10 (1)	0	8 (4)	0	**<0.01**	8 (6)	8 (3)	0.80
BVRT errors		16	3 (4)	0	11 (8)	15	**<0.01**	9 (7)	12 (11)	0.30
TOL		15	25.5 (5.5)	0	21.0 (9.0)	20	**0.01**	23.0 (7.0)	17.0 (15.0)	0.19
WCST		4	6 (1)	20	4 (4)	55	**0.03**	4 (3)	3 (5)	0.49
PHO Fluency		17.35	30.55 (11.83)	0	22.90 (13.63)	15	**0.02**	24.00 (17.50)	20.60 (10.30)	0.30
SEM Fluency		7.25	19.13 (11.31)	0	16.38 (9.63)	0	0.52	20.25 (9.25)	14.75 (6.75)	0.09
JLO		18	27 (4)	5	25 (9)	15	0.30	21 (12)	25 (7)	0.67
ZUNG		50	46 (20)	40	51 (11)	55	0.24	49 (13)	58 (13)	0.01
STAI Y-1		50	39 (15)	25	43 (16)	30	0.49	38 (16)	45 (17)	0.60
STAI Y-2		50	43 (15)	40	46 (15)	30	0.50	43 (18)	48 (12)	0.60

Median (IQR), % under cut-off. Abbreviation: BW = backward; CW = Colored Words; BSRT = Buschke Selective Reminding Test; BVRT = Benton Visual Retention Test; DR = delayed recall; JLO = Judgement of Line Orientation; LTR = Long Time Retention; MMSE = Mini Mental State Examination; PHO = Phonologic; SEM = Semantic; TMT = Trail Making Test; TOL = Tower Of London; WCST = Wisconsin Card Sorting Test. Number of decimals in results equal to cut-off's decimals, p = Mann-WhitneyU significativity, in bold if p_{corr}<0.05 Finner step-down,
p comparison Controls-SCA, p** comparison OPCA-CA*

Tab. 3. Emotion recognition data of patients and controls

	Controls	SCA	p*	OPCA	CA	p**
EKMAN						
Correct emotion recognized	80 (10)	65 (18)	**0.01**	67 (23)	65 (22)	0.66
Anger	80 (40)	60 (30)	0.04	60 (10)	70 (50)	0.41
Fear	60 (30)	50 (40)	0.16	50 (50)	50 (40)	0.82
Sadness	90 (20)	50 (40)	**<0.01**	50 (50)	60 (40)	0.77
Happiness	100 (10)	100 (10)	0.28	100 (20)	10 (10)	0.66
Disgust	70 (20)	70 (30)	0.41	70 (30)	70 (30)	0.99
Surprise	90 (20)	80 (30)	0.68	80 (40)	90 (30)	0.18
TAMIETTO						
Correct emotion recognized	55 (22)	**37 (18)**	**<0.01**	**42 (18)**	**37 (25)**	0.82
Positive†	60 (30)	**40 (25)**	**0.01**	50 (30)	**35 (50)**	0.82
Negative‡	55 (35)	**35 (15)**	**0.01**	**35 (15)**	**40 (20)**	0.15
Neutral	60 (30)	**50 (40)**	0.20	**50 (50)**	**50 (40)**	0.77
Flirtatiousness†	70 (50)	**30 (50)**	**<0.01**	**40 (40)**	**30 (50)**	0.50
Admiration†	50 (40)	**40 (20)**	0.17	50 (20)	**40 (50)**	0.77
Arrogance‡	60 (50)	**40 (30)**	0.05	**40 (30)**	60 (30)	0.11
Guilt‡	40 (50)	**20 (30)**	**0.01**	**10 (30)**	**30 (40)**	0.50

Median (IQR), scores represent the percentage of correct answers. Tamietto positive emotions = †, negative emotions = ‡, in bold if 2 standard deviation from mean, p = Mann-Whitney U significativity, in bold if <0.05, p comparison Controls-SCA, p** comparison OPCA-CA*

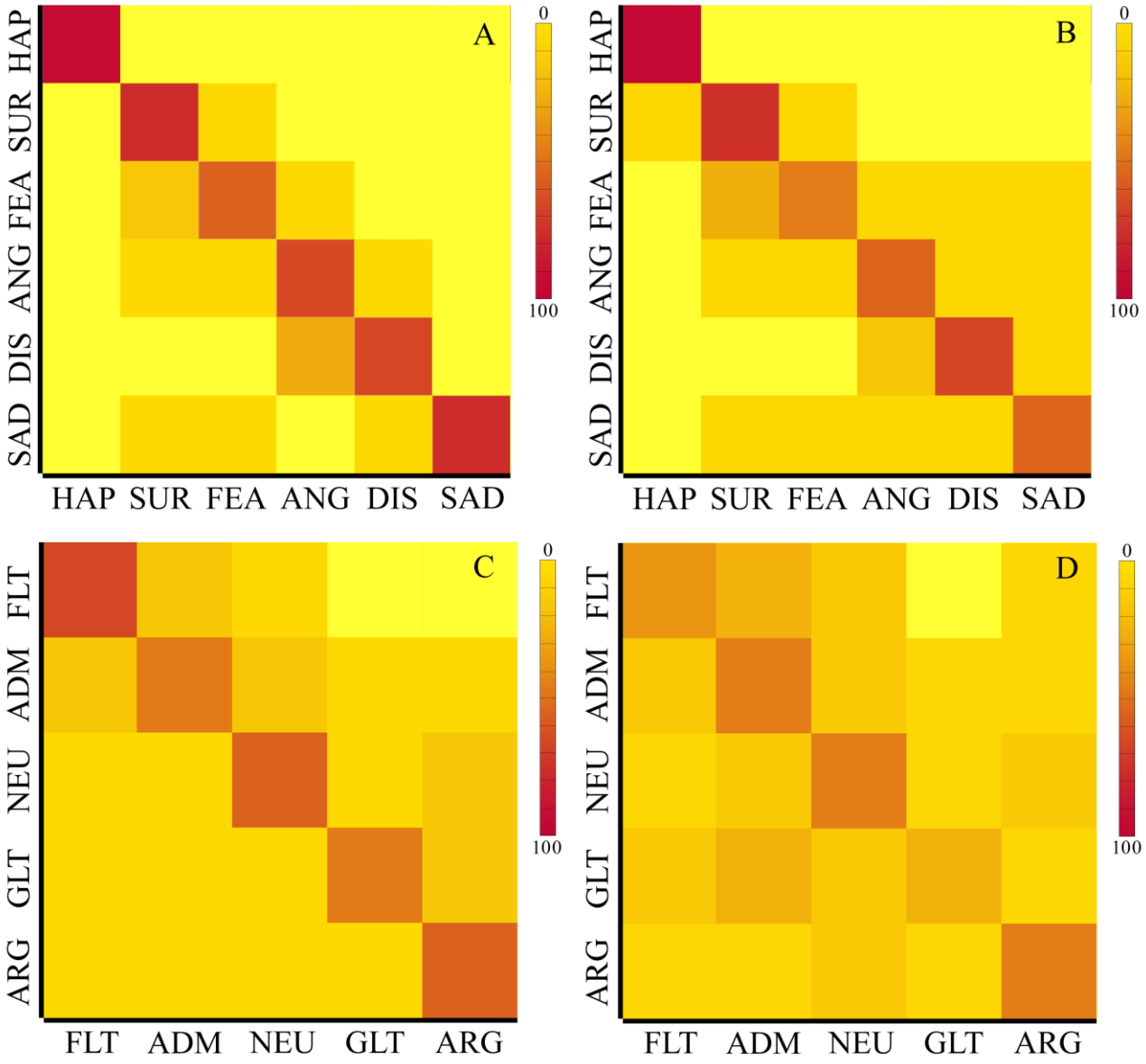
Tab. 4. SCA Correlations FDR corrected q≤0.05

TEST/ GROUP	EKMAN			TAMIETTO		
	SCA	**OPCA**	**CA**	**SCA**	**OPCA**	**CA**
TMT B	**-0.57**	**-0.86**	-0.48	-0.39	-0.44	-0.49
STROOP CW	**-0.69**	-0.57	-0.70	-0.34	-0.72	-0.20
DIGIT BK	**0.61**	0.49	0.65	0.46	0.25	0.57
BVRT errors	**-0.66**	**-0.84**	-0.69	-0.28	-0.31	-0.12
SEM Fluency	**0.55**	0.57	**0.82**	0.38	0.54	0.49
EDUCATION	**0.54**	0.54	0.63	0.37	0.57	0.29
EKMAN	-	-	-	**0.48**	0.49	0.47
TAMIETTO	**0.48**	0.49	0.47	-	-	-

Kendall Tau-b, in bold significative correlations

CAPTIONS

Fig 1. Recognition Matrix for Ekman and Tamietto tasks



The rows represented the faces presented to the participants, and was ordered by the similarity as perceived by normal subjects; The column represented how the stimuli were verbally recognized. The colours represent the percents of recognition or mismatching. Recognition Matrices: Ekman for controls (A) and SCA (B), Tamietto for controls (C) and SCA (D). Abbreviations: ADM = admiration; ANG = anger; ARG = arrogance; DIS = disgust; FEA = fear; FLT = flirtatiousness; GLT = guilt; HAP = happiness; NEU = neutral; SAD = sadness; SUR = surprise.