Characterizing daily-life social interactions in adolescents and young adults with neurodevelopmental disorders: a comparison between individuals with Autism Spectrum Disorders and 22q11.2 deletion syndrome

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Research

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Abstract

Background: Social impairments are common features of several neurodevelopmental conditions, including 22q11.2 deletion syndrome (22q11DS) and autism spectrum disorders (ASD). However, little is known about social interactions in daily-life. The Ecological Momentary Assessment (EMA) was used to have access to daily-life information and to distinguish the phenomenology of social interactions between the two conditions, often considered as presenting a similar profile of social impairments.

Methods: 32 individuals with 22q11DS, 26 individuals with ASD and 44 healthy controls (HC) aged 12-30 were recruited. All participants were assessed during 6 days 8 times a day using a mobile app. The EMA protocol assessed positive and negative affect, social context (alone versus in company) and the subjective experience of aloneness and social interactions.

Results: Participants with 22q11DS and ASD did not spend more time alone, but spent less time with familiar individuals such as friends, and more time with people they live with, compared to HC. However, distinct profiles emerged between the two conditions regarding the subjective experience of aloneness, with more intense feelings of exclusion in participants with ASD compared to participants with 22q11DS and HC. The subjective appreciation of interactions revealed that individuals with ASD felt more judged and more nervous than both 22q11DS and HC. Nevertheless, both conditions expressed a higher desire to be alone when in company of other people than HC.

Conclusions: This study highlights distinct social functioning profiles in daily-life in 22q11DS and ASD, giving new intel regarding the social phenotype in these conditions, and pointing towards different therapeutic targets.

Introduction

Social impairments are common features of several neurodevelopmental conditions, including 22q11.2 deletion syndrome (22q11DS) and autism spectrum disorders (ASD). 22q11DS is a neurogenetic condition affecting 1:2000–4000 live births and is associated with a broad phenotype of clinical and behavioral characteristics (1,2). Individuals with 22q11DS present social functioning impairments in terms of adaptive behavior, social inhibition and isolation from peers (3–5), but also in social skills (6,7). These social difficulties, especially social withdrawal, tend to become more pronounced during adolescence (8). In ASD, a neurodevelopmental disorder affecting 1:100–200 individuals and characterized by alterations in social communication and interactions, altered social interactions appear very early on and remain stable with age, inducing difficulties in social reciprocity as well as in initiating and maintaining social interactions and relationships (9–12). These deficits in social functioning and social skills can lead to lower social participation and higher isolation that are associated with broad negative consequences and poor long-term outcomes (3,13–16). Adolescence, being a transition phase between childhood and adulthood, is a particularly relevant developmental period to investigate social interactions. In particular, it appears that socialization during adolescence, notably the growing emphasis

on interactions with peers and the mounting complexity of social relationship (e.g., 17), is crucial for the outcome of teenagers. Indeed, several studies have shown that social support during adolescence is important in mediating stress (e.g., 18), as well as for mental health outcomes and quality of life (19,20,e.g., 21). Whereas it is well acknowledged that ASD and 22q11DS are characterized by social impairments, little is known about the exact nature of social difficulties during the developmental period of adolescence.

In this regard, recent studies (e.g., 22) highlighted the importance of differentiating between objective and subjective aspects of interactions, namely “social behaviors”, that are quantifiable but that take away individual perspective (e.g. percentage of time spent alone), versus “social experiences” that are more experiential (e.g. how individuals subjectively experience their interactions with others). This distinction is relevant to consider since it has been found that subjective aspects of social interactions do not necessarily relate to objective aspects (23) and that subjective aspects might be more strongly related with outcome in adolescents (22). So far, some studies point towards differences in *social behaviors* in individuals with ASD and in 22q11DS (e.g., 24). For instance children with ASD spend half as much time with their peers compared to healthy controls (HC) (25) and very few adults with ASD have had a long-term relationship (26). Individuals with 22q11DS have frequently been described as shy and more withdrawn from their peers than HC (27,e.g., 28), but there is no comparable study about relationships to our best knowledge. However, the current literature remains scarce in terms of *social experiences*. For instance, it is still unclear if individuals with ASD and 22q11DS like being alone or feel lonely (e.g., 29), and whether they spend more time alone because they lack interest to be with others or because they experience aversive feelings during interactions (e.g., 30). Thus, little is known about the subjective experiences of social interactions and it appears of crucial importance to get a better comprehension of the phenomenology of these interactions.

As *social experiences* are ephemeral and context dependent, it seems particularly necessary to find a way to observe how interactions are lived by people in real-life in the most naturalistic way. Henceforth, the Ecological Momentary Assessment (EMA) – a structured diary technique that collects real-life measures in the everyday-life context (31) – appears to be a suitable technique to investigate social interactions in daily-life with high ecological validity. Moreover, EMA has several advantages, including multiple and in-the-moment assessments per day, which overcomes the problem of retrospective recall bias and the low correspondence that can be observed with paper-pencil questionnaires and interviews (32–34). It also captures fluctuation of the measured constructs such as emotional variability, and collects information in a natural setting that reflects real life. Moreover, EMA gives access to the impact of context on affective states, which deepens the link between environmental context and its influence on internal states (31,32). Of note, this method was found reliable to assess vulnerable populations, such as individuals with intellectual disability (35) or schizophrenia (36–38). To the best of our knowledge, this technique has only been used twice in adults with 22q11DS to characterize affective and psychotic reactivity to daily-life stress (39,40). In individuals with ASD, there is a paucity of studies (41–49), most of them focusing on the feasibility of the EMA technique. However, Hintzen and al. (45) found that adults with ASD did not spend more time alone and did not report an increased preference for being alone compared to a control

group, pointing toward a preserved desire to be in interaction with others. However, they expressed more negative affects when in the company of less familiar people compared to when they were alone, suggesting that social interactions outside of the direct family context can trigger negative affective states (45). In addition, Chen and al. (47) highlighted that adolescents and adults were motivated to engage in social interactions in contexts where they felt competent and didn't experience difficulties. Altogether, these results suggest a relatively preserved desire to interact with other people in individuals with ASD as well as a significant influence of the social context on affective states and motivation. However, these studies involved small samples (between 6 and 8 participants), highlighting the need to further investigate social experiences in daily life.

In the present study, EMA was used to characterize social functioning in the daily-life of adolescents and young adults with 22q11DS and ASD. Being alone or in the company of others as well as the subjective experience of these two contexts was investigated. In terms of *social behaviors*, we expected individuals with ASD and 22q11DS to spend more time alone than HC, more time with the persons they are living with, and less time with familiar persons not living with them as well as unfamiliar persons. In terms of *social experiences*, exploratory hypotheses were made because of the paucity of studies available in the literature. Therefore, we expected individuals with ASD and 22q11DS to report a different experience of aloneness (ExpA) and social interactions (ExpSI) compared to HC. Finally, we also expected that the social context (alone vs. with other people) would have a different influence on positive (PA) and negative affect (NA) in ASD and 22q11DS compared to HC.

Method

Sample

One hundred and seven participants (46% female) aged between 12 and 30 were included in the study (mean age = 18.54, SD = 4.28). Twenty-eight (46% female) individuals with ASD (mean age = 18.20, SD = 4.98) were recruited in clinical centers in Geneva and France and through announcements to family associations in Switzerland and France. Thirty-three (42% female) 22q11DS carriers (mean age = 19.19, SD = 4.67) were recruited through the 22q11DS Swiss longitudinal cohort. Forty-six (48% female) individuals were part of the HC group (mean age = 18.27, SD = 3.51) and were recruited through announcements at the University of Geneva and through the siblings of the 22q11DS individuals. Written consent was asked from caregivers for all participants with ASD and 22q11DS, as well as for HC under 18 years. This study was approved by the Swiss Ethics Committee on research involving humans (Commission Cantonale d'Ethique de la Recherche sur l'Etre Humain – CCER) in Geneva (CH).

Inclusion criteria for all participants were 1) age between 12–30 years and 2) sufficient command of the French language. All participants from the ASD group had a confirmed clinical diagnosis of ASD. They were assessed both with the Autism Diagnostic Observation Schedule, second version (ADOS-2;(50)), and their caregivers with the Autism Diagnostic Interview-Revised (ADI-R;(51)) or the Social Communication Questionnaire (SCQ;(52)). All participants from the 22q11DS group had a confirmed genetic diagnosis of

microdeletion 22q11.2. They were screened with the Social Communication Questionnaire (SCQ; (52)) with a mean score of 7.08. Six participants with 22q11DS had a score above the clinical cutoff (15). Both ASD and 22q11DS individuals were screened with a validated semi-structured instrument for comorbid psychiatric disorders. Comorbidities, medication and ASD scores are displayed in Table 1. Note that all participants were assessed with children or adults Wechsler intelligence scales (WISC-V;(53) or WAIS-IV; (54)) but intellectual deficiency was not an exclusion criterion since EMA can be used in populations presenting cognitive impairments (35). For HC, exclusion criteria were 1) being born preterm, 2) having a first degree relative with any developmental disorder (siblings of participants with 22q11DS were included if the 22q11.2 deletion was confirmed to be de novo), 3) having a lifetime history of psychiatric (including neurodevelopmental disorders such as ASD), neurologic or learning impairments. Of note, HC were screened using the SCQ, with a mean score of 2.57 and none of the participants scoring above the clinical cutoff. Sample characteristics are displayed in Table 1.

Procedure and assessment

The current research was carried out as part of a larger study also involving other tasks that are not described in the current study. Participants received a voucher of 100 swiss francs (FNAC) or of 90 euros (amazon) for their participation to the study, regardless of their compliance to the EMA protocol. Participants, as well as their parents for ASD and 22q11DS participants and HC under 18 years old, were briefed about the EMA procedure (number of days, types of questions, etc.). The RealLife Exp app was then installed on the participants' smartphone and a trial questionnaire was completed with a member of the research team to obtain clarification if necessary. For younger participants and participants with cognitive difficulties, a trial questionnaire was also shown to the parents so that they could provide help if necessary (e.g., reminder of the meaning of a word). The EMA protocol was then carried out by the participants, with messages from the researchers every two days to verify study compliance and encourage participants. A clinical report was sent to ASD and 22q11DS participants to give them a feedback and suggest psychoeducational arrangements depending on their answers.

The EMA protocol lasted for 6 days, with semi-random signal-contingent notifications 8 times per day between 7.30 AM and 10 PM. A minimum time window of 30 minutes was scheduled between two consecutive beeps. Participants had a maximum of 15 minutes to start completing the questionnaire, and an unlimited amount of time to fill out the questions. However, and this was not specified in the co-registration (osf.io/g4hv6), only the beeps that corresponds to a session length below 15 minutes were kept to ensure that participants' answers correspond to the moment they were assessed (i.e. *in-the-moment* assessments). At each notification, the same momentary EMA questionnaire was delivered. It consisted of a minimum of thirty-three items and a maximum of thirty-eight items, depending on the answers to conditionally branched questions. There were no open-ended questions. PA (happiness, self-confidence, excitement, relaxation) and NA (sadness, anxiety, loneliness, anger) were assessed with a series of items, answered by a Likert scale ranging from 1 (not at all) to 7 (extremely). Participants then had to report whether they were alone (non-social context) or in company of other persons (social context). They could report to be with up to three different types of company. Context was divided in four

categories: 1) alone; 2) people they are living with (including pets); 3) familiar persons they don't live with (family members; boyfriend/girlfriend; friends; colleagues/classmates); 4) unfamiliar persons (health professionals, acquaintances, strangers). When participants reported to be with several categories of people, the more familiar person was chosen (for instance if a participant reported to be with someone he was living with and a friend, we recoded it as "people they live with": people they live with > familiar > unfamiliar). Of note, when individuals were living with their boyfriend or girlfriend, the category "someone I live with" was chosen. If participants reported to be alone, they were asked about their ExpA (aloneness appreciation, isolation and rejection feelings, desire to be with other people). On the contrary, they had to report their ExpSI (company appreciation, judgement and nervousness feelings, desire to be alone) when they were in company of other people. Of note, principal components analyses were performed to ensure that the items composing the different variables (i.e., PA, NA, ExpA and ExpSI) loaded on a single component (values above > .30). See Table 2 for EMA items and details about how they were aggregated into variables. In line with previous studies and general recommendations (31,55), only participants who answered to at least one-third of the beeps were kept in the analyses. A total of 5 participants were excluded from the analyses for this reason (n = 2 individuals with ASD, n = 1 individuals with 22q11DS, n = 2 HC). The final sample used for the analyses is therefore composed of 102 individuals (n = 26 ASD individuals with 880 valid notifications, n = 32 22q11DS individuals with 983 valid notifications, n = 44 HC with 1413 valid notifications).

Statistical Analysis

Statistical analyses were conducted in STATA version 16.0. For all analyses, the level of statistical significance was set to $p < .05$. Analyses of variance (ANOVA) and chi-squared tests were used to investigated group differences in age, gender and IQ.

The data have a two-level structure: repeated measurements (level 1), nested within individuals (level 2). Multiple linear regression models were performed for group comparisons for time-invariant variables (*i.e.* one observation per participant, such as the percentage of time spent alone), using the REGRESS command. We controlled for age, gender and period of answers (*i.e.* holidays vs school/work). Note that we chose not to use IQ as a covariate since lower IQ is part of the phenotype of many neurodevelopmental disorders. Therefore, covarying for IQ would remove some of the variance inherent in the diagnosis (56). Multilevel regression analyses were performed to compute group differences in time-varying variables (*i.e.* one observation per beep for participant, such as happiness). More specifically, mixed effects models with random intercepts were performed for group comparisons with the time-invariant categorical variable "group" used as a predictor and the time-varying continuous variables ExpA and ExpSI used as outcomes at the momentary level, using the XTSET/XTREG command. Mixed models with the time-invariant categorical variables "group", "company" and "group*company" used as predictors and the time-varying continuous variables PA, NA and ExpSI used as outcomes at the momentary level were also performed to assess the impact of the different type of company, using the XTMIXED command. The B's represent the fixed regression coefficients of the predictors in the multilevel model.

This study was co-registered on the OSF platform (osf.io/g4hv6) and the data are available open access on the Yareta preservation system. Two deviations from the original statistical analysis plan have to be noted. First, to improve the coherence of the study, we decided to exclude the results related to motivation (hypotheses H5a, H5b and H5c from the co-registration form) and they will be reported in a distinct paper. Secondly, an additional analysis was included in this paper to examine the modulation of affect (PA and NA) by the context (alone vs. with others) and the group (22q11, ASD, and HC) as well as the context*group interaction. This was done using mixed models with the time-invariant categorical “group”, “context” and “group*context” used as predictors and the time-varying continuous affect variables PA and NA used as outcomes at the momentary level using the XTMIXED command.

Results

Sample (EMA) characteristics

The three groups were not statistically different in terms of age and gender but both participants with ASD (F (1, 55) = 79.817, p < 0.001) and HC (F (1, 68) = 158.532, p < 0.001) differed from 22q11DS on full-scale IQ scores. This was expected, given that impaired cognitive functioning is a core characteristic of individuals with 22q11DS. The average IQ level in the 22q11DS group was 71, which corresponds to what is typically reported in this population (e.g., 57). The ASD group reflects the high functioning part of the spectrum since the mean IQ was 108, with only 2 (8%) participants having an IQ in the intellectual disability range (IQ < 70). Of note, 6 participants with 22q11DS scored above the clinical cutoff on the SCQ. To investigate the impact of participants with an elevated SCQ score on the obtained results, all the analyses were conducted while excluding these 6 participants and the results remained unchanged. The results reported below therefore include these 6 participants. Values are displayed in Table 1.

Group differences on social behaviors

There was no difference across the three groups regarding the percentage of time spent alone (22q11DS vs HC: (b = .634 (95% CI -10.017 to 11.286), p = .906); ASD vs HC: (b = 5.715 (95% CI -5.545 to 16.976), p = .316); 22q11DS vs ASD: (b = 5.372 (95% CI -5.942 to 16.687), p = .345)).

Compared to the control group, both 22q11DS individuals (b = 15.775 (95% CI 4.786 to 26.764), p = .005) and ASD individuals (b = 23.483 (95% CI 4.866 to 24.101), p = .035) spent more time with people they live with compared to HC. There was no significant difference between the two clinical groups (b = -3.057 (95% CI -15.301 to 9.187), p = .619). Conversely, participants with 22q11DS (b = -16.637 (95% CI -26.072 to -7.201), p = .001) and ASD (b = -19.281 (95% CI -29.356 to -9.306), p = .000) both spent less time than HC with familiar individuals. There was no significant difference between the two clinical groups (b = -312 (95% CI − 11.508 to 5.252), p = .457). To examine the different types of company within the category of familiar individuals, *post-hoc* analyses were conducted and revealed that 22q11DS and ASD individuals both spent less time with friends (22q11DS: (b = -8.790 (95% CI -15.529 to -2.052), p = .011) ASD: (b = -9.396 (95% CI -16.520 to -2.273), p = .010)) and with boyfriends/girlfriends (22q11DS: (b = -9.477 (95% CI -14.131 to -4.824), p = .000) ASD: (b = -7.101 (95% CI -12.020 to -2.181), p = .005)) than HC.

However, there was no difference regarding the percentage of time spent in the company of relatives they don't live with, nor in the time spent with classmates/colleagues (all p > 0.5). Finally, no statistical differences appeared between the three groups regarding the percentage of time spent with unfamiliar individuals (22q11DS vs. HC (*b* = .231 (95% CI -1.910 to 2.372), *p* = .831); ASD vs. HC (*b* = .966 (95% CI − 1.297 to 3.229), *p* = .399); 22q11DS vs ASD: (*b* = .683 (95% CI − 1.932 to 3.319), *p* = .598)). The variables of interest's mean values are displayed in Table 3.

Group differences on social experiences

a) Experience of aloneness (ExpA)

Regarding ExpA, no significant difference was found between the three groups (HC vs ASD (*b* = .052 (95% CI − .390 to .495), *p* = .818); HC vs 22q11DS (*b* = .142 (95% CI − .284 to − .390), *p* = .512); ASD vs. 22q11DS (*b* = − .092 (95% CI − .587 to .403), *p* = .715). However, when comparing the groups on the individual items composing ExpA, we observed that individuals with ASD felt more excluded than HC (*b* = .755 (95% CI .357 to 1.152), *p* = .000), but not than 22q11DS (*b* = .495 (95% CI − .064 to 1.054), *p* = .083). There was no difference between HC and 22q11DS (*b* = .285 (95% CI − .098 to .669), *p* = .145). No difference appeared in the preference to be with others between the groups (HC vs 22q11DS (*b* = .203 (95% CI − .440 to .846), *p* = .536), HC vs 22q11DS (*b* = − .275 (95% CI − .941 to .390), *p* = .536), 22q11DS vs ASD (*b* = − .493 (95% CI -1.177 to .190), *p* = .157)). Finally, there was no difference in the appreciation of aloneness between the groups (HC vs 22q11DS (*b* = − .050 (95% CI − .781 to .679), *p* = .892), HC vs 22q11DS (*b* = − .322 (95% CI -1.080 to .434), *p* = .404), 22q11DS vs ASD (*b* = − .286 (95% CI -1.127 to .555), *p* = .505)). The variables of interest's mean values are displayed in Table 3.

b) Experience of social interactions (ExpSI)

Participants with ASD reported a significantly worse subjective appreciation of social interactions (ExpSI) than both HC (*b* = .863 (95% CI .596 to 1.130), *p* = .000) and participants with 22q11DS (*b* = .660 (95% CI .321 to .999), *p* = .000). HC did not differ from 22q11DS (*b* = .208 (95% CI − .045 to .461), *p* = .107). Looking at each item composing ExpSI individually, participants with ASD reported feeling significantly more judged than both HC (*b* = .605 (95% CI .378 to .832), *p* = .000) and participants with 22q11DS (*b* = .503 (95% CI .212 to .794), *p* = .001). HC did not differ from 22q11DS (*b* = .106 (95% CI − .109 to .322), *p* = .333). They also reported to feel more nervous in the company of other people compared to both HC (*b* = .831 (95% CI .531 to 1.130), *p* = .000) and participants with 22q11DS (*b* = .737 (95% CI .333 to 1.141), *p* = .000). HC did not differ from 22q11DS (*b* = .101 (95% CI − .182 to .386), *p* = .482). Participants with ASD also rated the company of people they were with to be less pleasant than both than HC (*b* = .923 (95% CI .489 to 1.358), *p* = .000) and participants with 22q11DS (*b* = .940 (95% CI .424 to 1.456), *p* = .000). HC did not differ from 22q11DS (*b* = − .011 (95% CI − .423 to .401), *p* = .957). Finally, individuals with ASD (*b* = 1.086 (95% CI .617 to 1.554), *p* = .000) and 22q11DS (*b* = .637 (95% CI .193 to 1.081), *p* = .005) both reported that they would prefer to be alone while with others to a greater extent than HC. The two clinical groups did not differ from each other regarding this specific item (*b* = .453 (95% CI − .178 to 1.085), *p* = .160). Overall, participants did not report a change in ExpSI depending on the company type (*b* = − .172

(95% CI − .364 to .021), p = .081). Moreover, the ExpSI * company type interaction was not significant, indicating that the impact of the company type on ExpSI was similar between the groups (all p > 0.5). The variables of interest's mean values are displayed in Table 3.

Influence of context on affects

On average, participants with ASD reported more NA overall than HC (b = .578 (95% CI − .205 to .952), p = .002), regardless of the context. 22q11DS did not differ from ASD (b = .358 (95% CI − .142 to .861 .952), p = .161) nor from HC (b = .231 (95% CI − .122 to .584), p = .199) on NA level. All participants reported more NA when alone compared to when in company of other people (b = .160 (95% CI .956 to .263), p = .002). However, the group * context interaction was not significant (all p > .05), indicating that the association between NA and the social context was similar in the three groups. Overall, participants did not report a change in NA depending on the company type (b = − .034 (95% CI − .171 to .103), p = .628). Moreover, the group * company type interaction was also not significantly associated with NA, indicating that the type of company did not influence NA differently in the three groups (all p > .05). Mean levels of NA are displayed in Table 3.

On average, participants with ASD reported less PA overall than HC (b = − .611 (95% CI -1.034 to − .188), p = .005), regardless of the context. 22q11DS did not differ from ASD (b = − .491 (95% CI − .994 to .012), p = .056) nor from HC (b = − .114 (95% CI − .514 to .285), p = .574) on PA level. Participants did not report a change in PA when alone compared to when in company of other people (b = − .099 (95% CI − .211 to .021), p = .081). However, the group * context interaction was significant between HC and 22q11DS (b = .174 (95% CI .000 to .349), p = .050), indicating that individuals with 22q11DS reported significantly higher PA when alone and lower PA when in company of others, the opposite pattern being observed in HC. ASD did not differ from HC, nor from 22q11DS (p > .05). Overall, participants did not report a change in PA depending on the company type (b = .146 (95% CI − .054 to .347), p = .154). The group * company type interaction was not significantly associated with PA, indicating that the type of company did not influence PA differently in the three groups (all p > .05). Mean levels of PA are displayed in Table 3.

Discussion

This is the first study to characterize social functioning in daily-life in a relatively large sample of adolescents and young adults with ASD and 22q11DS using EMA. Our main findings indicate that both participants with ASD and 22q11DS show similar *social behaviors.* In particular, they spent a comparable amount of time alone, more time with the people they live with but less time with familiar individuals (*e.g.*, friends) than HC. Overall, participants with ASD and 22q11DS also reported a similar experience of aloneness (*ExpA*), with the exception that individuals with ASD reported feeling more excluded than both participants with 22q11DS and HC. By contrast, they reported markedly different social experiences (*ExpSI*), with individuals with ASD reporting worse ExpSI than both participants with 22q11DS and HC. The only similarity between the two clinical groups in terms of ExpSI was a higher desire to be alone when in company of other people compared to HC. Regarding *the influence of context on affect*, individuals with ASD reported less PA and more NA than the other two groups, regardless of the context.

Finally, being in the company of other people had a beneficial impact on affect in HC, whereas this benefit was less clear in 22q11DS.

Social behaviors

The present study challenges the commonly accepted idea that social withdrawal is a characteristic of neurodevelopmental disorders (4,15,16,24,25,58), as the three groups reported spending a similar amount of time alone (*i.e.* physical absence of other people or *aloneness* (59)). This is however in line with the findings of Hintzen and al. (45), who also used EMA, whereas the remaining studies used more classical approaches to measure social withdrawal, such as questionnaires and interviews. Moreover, the majority of studies used information reported by caregivers and not by the participants themselves. That being said, even if the present study highlights a comparable amount of time spent alone between the three groups, it also suggests that individuals with 22q11DS and ASD have a different involvement in the social world compared to their typically developing peers. Indeed, they both reported spending more time with the people they live with and less time in the company of familiar persons outside of the direct family circle, friends in particular. However, a similar amount of time spent with classmates and colleagues was reported between the groups. This is in line with previous studies reporting smaller social networks in individuals with ASD (13,60–63) and the fact that individuals with 22q11DS have been described to be more isolated from peers (4). These results also highlight the central role of the family environment in the lives of adolescents and young adults with neurodevelopmental disorders (e.g., 64). During development, adolescence typically represents a period of emancipation from the family circle (65), a process that appears to be challenged in both youth with 22q11DS and ASD. Several reasons could potentially explain this phenomenon.

First and in line with previous reports (e.g., 66), it suggests that individuals with 22q11DS and ASD have fewer opportunities of interactions, especially in less structured environments, which may prevent them from broadening their social network. Indeed, the fact that participants with 22q11DS and ASD reported spending a comparable amount of time with classmates or colleagues than their peers is probably explained by the fact that these interactions mostly take place in relatively structured contexts (*e.g.*, school or work). These interactions might therefore be more predictable and more accessible than those one can have with friends. Of note, the majority of our sample was composed of people who were still attending school, which ensures at least a minimal number of social encounters through these structured contexts. This should be considered in light of the transition to adulthood, a period during which there might be less structured opportunities to be in contact with other people outside of the direct family circle. Indeed, several studies have highlighted a high percentage of unemployment among adults with ASD (67–69), especially younger adults (70), which reduces the opportunities of interactions in a structured environment. Of note, this phenomenon might be a shared characteristics of several clinical populations, including individuals with neurodevelopmental disorders and severe mental illness such as schizophrenia (71). This lack of opportunity to interact with peers, especially in less structured settings, may be related to the fact that social initiatives are more difficult for youth with ASD and 22q11DS. Incidentally, adolescents with ASD were found to rely more on parents to facilitate social relationships (14,25,72),

which would mean that they spend time with family members in order to access time with friends. In the present study, the different types of company were computed to be mutually exclusive. For this reason, we could not identify if participants reported to be in the company of both a family member and a friend, which could support the idea of family as a way of accessing friends. Moreover, cognitive level was found to account for spontaneous initiations of interaction with peers (25). Particularly in the group of participants with 22q11DS, whose average intellectual functioning level is in the borderline range, this could contribute to explain the differences in the time spent with friends. Indeed, interactions with friends mostly take place in less structured contexts and therefore rely more on the ability to actively initiate an interaction and less on the ability to follow well defined “social scenarios”.

Secondly, it is possible that when HC refer to people as “friends”, individuals with ASD and 22q11DS refer to them as “classmates/colleagues”. Indeed, this distinction requires a deep and accurate understanding of the different types of relationships as well as a certain introspection to fully gasp the distinction between the different kind of relationships. Incidentally, it was found that children with ASD lack an intersubjective understanding of interactions with peers and social relationships when they were asked about the quality of their relationships and about their understanding and feelings of loneliness with self-report questionnaires about friendship and loneliness (73), which makes it hard to fully understand the complexity of social interactions. Interestingly, the number of friends reported by the caregivers were superior of the one reported by the children in the study of Bauminger & Kasari (73). This is in line with the precited hypothesis of a misunderstanding of the different degree of friendship and the derived terms (*e.g.*, friend or classmate).

In summary, the present study shows that individuals with 22q11DS and ASD are not characterized by social withdrawal as such but that social interactions take place much more within the restricted family circle and in relatively structured environments. Since most of our participants were still attending school – which provides opportunities for structured social interactions – the results of the present study suggest that the transition after school and towards independent living should also be anticipated from a social perspective in order to avoid a decrease of the number of social contacts. A longitudinal follow-up of such a cohort would provide a unique opportunity to investigate how social behaviors evolve during this transition period from adolescence to adulthood.

Social experiences

Experience of aloneness (ExpA)

Contrary to our expectations, the three groups reported a similar subjective experience of aloneness. This is a major finding considering that, as previously said, social disinterest is typically considered to be a feature of both ASD and 22q11DS (e.g., 24,74). Taken together, the results of this study suggest that individuals with 22q11DS and ASD are not characterized by social withdrawal from a quantitative point of view (*i.e.* social behavior) but also do not report social disinterest from a qualitative point view (*i.e.* social experiences). Moreover, it is particularly interesting to note that the three groups did not differ on the item “I’d rather be with other people”, pointing toward a preserved, but of a relatively low intensity,

motivation for interpersonal interactions, as pointed out by previous studies (25,75,76). It should be noted that the findings discussed in the context of the present study are based on group comparisons that may mask substantial interindividual variability. Future studies should aim to parse this heterogeneity in order to identify relevant subgroups of individuals characterized by distinct social profiles. Such an approach has recently been employed by Uljarevic et al. (77) who used a social functioning questionnaire to cluster individuals with ASD based on their social phenotype. However, given the limitations of classical measures of social functioning to assess social experiences in an ecologically valid way (34), future studies may use EMA to identify more relevant subgroups.

Despite an overall similar subjective experience of aloneness among the three groups, individuals with ASD reported higher levels of exclusion and isolation feelings than both participants with 22q11DS and HC when looking at individual items composing ExpA one by one, which points towards increased loneliness (*i.e.* a negative emotional experience (59)) in this population. These findings are in line with previous studies that found higher levels of loneliness in younger (14,25,e.g., 63,73,78) and older adolescents with ASD (e.g., 29,79,80), though none of them used EMA to measure this construct. As suggested by Maddox and al. (76), the subjective feeling of social isolation experienced by individuals with ASD could be explained by a lack of knowledge about how to form relationships. Besides, it was shown that adolescence is a transition phase during which individuals experience new relationships and the expectations towards these relationships evolve (81), inducing loneliness when there is a gap between the expectations and reality (59,82). Interestingly, one of the few studies that directly compared individuals with ASD and 22q11DS found higher levels of empathy, sense of humor and other complex social skills in 22q11DS than in idiopathic ASD (83), elements that could possibly play a role in preventing them to feel lonely. Indeed, if individuals with ASD have little access to these complex social skills, it could lead to a worse comprehension of social interactions, and therefore to feelings of rejection and a greater experience of loneliness. Of note, social anxiety was also found to be related to greater loneliness (78,84–88), and this comorbidity was reported twice as much in our sample of individuals with ASD compared to the 22q11DS group, playing a plausible role in explaining the distinct experience of aloneness between the two conditions. Moreover, social anxiety was described by Hintzen et al. (45) as the discrepancy between the fear of rejection and the desire for social interaction, a pattern that matches what is reported by individuals with ASD in the present study. Future studies should aim to better investigate loneliness in individuals with ASD and with 22q11DS by taking in account the potential impact of social anxiety.

Experience of social interactions (ExpSI)

Contrary to the experience of aloneness, participants with ASD reported a markedly different – and more negative – experience of social interactions than both individuals with 22q11DS and HC, providing information about *how* social interactions are experienced in daily-life and not only about the quantity of social interactions. This finding is not consistent with the previous report of Hintzen and al. (45), who observed that individuals with ASD mostly enjoyed the company of other people. This could be explained by the fact that our sample, being younger than the one of Hintzen and al. (mean age = 28.3), is

characterized by less mature emotion regulation strategies. Indeed, the latter are known to improve with age (89), and in younger sample like ours, could contribute to the rather negative experience of social interactions. Additionally, emotion regulation difficulties have been shown to be inherent to ASD and contribute to the socioemotional and behavioral problems they experience (e.g., 90). The period of adolescence is also characterized by more conflictual social interactions (e.g., 91), and experiences of bullying and peer victimization appear to be particularly frequent among individuals with ASD at this age (e.g., 92). A longitudinal follow-up of this cohort of adolescents and young adults would allow to investigate whether changes in the experience of social interactions are occurring with increasing age.

Of particular interest, the present study highlights that the subjective experience of social interactions is markedly different between individuals with ASD and those with 22q11DS, with subjective reports of ExpSI in the 22q11DS group being similar to those of HC. Besides, if ASD has been described as a frequent comorbidity of 22q11DS (e.g., 93), other studies also highlighted differences between the two conditions in terms of social impairments (83,94,95). Moreover, previous findings suggests that individuals with both 22q11DS and ASD are characterized by social anhedonia (96–98), described as a diminished social interest and a lack of pleasure from social contact leading to withdrawal (99). However, the present study offers new insights regarding the subjective experience of social interactions that challenge this assumption. As already stated above, these discrepancies might arise from the fact that previous studies used parent-reported information collected in a laboratory setting, whereas the present study uses self-reported information collected in the daily-life of individuals. In our sample of participants with ASD, the profile of answers was more characteristic of social anxiety than of a diminished social interest. Indeed, they reported a negative experience of social interactions and a lower enjoyment of the company of others compared to both participants with 22q11DS and HC, but did not spend more time alone. The reports of participants with 22q11DS during social interactions were also not indicative of a diminished social interest, as they experienced social interactions rather positively and rated the pleasantness of their social company similarly to HC. When alone, they also reported wanting to be with other people to the same extant than HC, which is also suggestive of a preserved motivation to interact with others. Of particular interest, recent studies using EMA have also challenged the notion of social anhedonia in psychosis. In particular, adults with psychosis were found to spend less time with other people than HC but reported an intact hedonic experience of social interactions (71), a profile that is relatively consistent with the one observed in our sample of participants with 22q11DS. Of note, ExpSI was not influenced by the type of company in any of the three groups, suggesting that profile described above reflect how participants experienced their social interactions *in general*. However, it should be noted that the small number of occurrences during which participants were in company of unfamiliar people prevented us of examining ExpSI in this social context specifically. In line with previous studies (e.g., 45), it is likely that they would have resulted in a more negative ExpSI.

Interestingly, both participants with ASD and 22q11DS reported a greater preference for being alone when they were in the company of other people, regardless of the type of company. Incidentally, this was the only significant difference between individuals with 22q11DS and HC, who otherwise reported a similar positive appreciation of social interactions. This could possibly be explained by the cost of interacting:

for individuals with ASD or 22q11DS, social interactions might require greater efforts than for HC, hence the higher desire to be alone, although social interactions were not as unpleasant for 22q11DS as they were for ASD. Of note, since participants with 22q11DS and ASD spent more time with the people they live with, it is also possible that they did not always choose to be interacting with them, contributing to this higher wish to be alone.

Altogether, the results regarding social behaviors and the subjective experience of social interactions suggest that individuals with 22q11DS and ASD could benefit from different therapeutic intervention targeting social impairments. Indeed, individuals with 22q11DS should probably be supported on how to initiate and maintain social interactions since they experience social interactions positively but experience difficulties in this domain. In ASD, interventions should rather focus on skills that might help to decrease the negative experiences of social interactions, such as increasing conversational skills. Support could also be offered on how to better discriminate and differentiate other people's affective states during social interactions, which may increase interpersonal synchrony and contribute to experience social interactions in a more positive way. For example, it has been shown that a poor differentiation of other people's emotions in individuals with ASD contributed to lower levels of empathy and to mimic the facial expression of others to a lesser extent (e.g., 100). Moreover, interventions targeting social anxiety have been proven to be benefic and even more effective when coupled with social skills training (e.g., 101).

Influence of context on affect

Individuals with ASD reported less PA and more NA than 22q11DS and HC, regardless of the context. Therefore, ASD participants reported a more negative emotional experience overall, whether they were alone or in company of other people. This is in line with several findings in autism that revealed intense negative and attenuated positive emotions (102,e.g., 103), although divergent findings have also been reported (104). The relatively high level of NA could partially be accounted by the psychiatric comorbidities present in our ASD sample: mood disorders were reported twice as much by participants with ASD than by participants with 22q11DS, the same being observed for social phobia and agoraphobia.

In the HC group, being in the company of other people was shown to have a beneficial impact on affective states. Indeed, higher levels of NA and lower levels of PA were observed when alone, the oppositive pattern being found when in the company of others. This is in line with a study using EMA that found more happiness and interest, as well as less sadness, pain and tiredness when individuals were engaged in social interactions as opposed to when they were not (e.g., 105). In individuals with 22q11DS, this benefit was less clear since the social context had a similar impact on NA than in HC but an opposite impact on PA. The fact that reduced NA were reported in both HC and 22q11DS when in company of others highlights the positive impact of being with others on NA. This is coherent with the positive ExpSI reported by both HC and 22q11DS, indicating that interactions with others were enjoyed and associated with lower NA. Of note, 22q11DS spent the majority of their time with people they live with, meaning that interactions took place in a structured and well-known environment that was probably reassuring and

could have soothed NA. However, PA were higher when alone in 22q11DS. This could be explained by the fact that, spending a lot of time home, participants with 22q11DS didn't necessarily always choose to be interacting with the people they live with, which could explain why they report greater PA when alone. Moreover, as already discussed, interactions probably required greater effort for participants with 22q11DS, which could contribute to making them feel more relaxed and joyful when alone.

Strengths, limitations and future directions

This is the first study comparing the social phenotype in daily-life of two neurodevelopmental conditions – ASD and 22q11DS. By using EMA, contextual information is taken into account and offers more granulated information that consider daily variations, therefore ensuring that participants' answers reflect their actual environment accurately. Moreover, it shows feasibility of this method in neurodevelopmental disorders, reinforcing EMA literature that is still scare in this domain. Furthermore, the present study contributes to better distinguishing between two conditions often considered as characterized by the same social impairments, adding new information about social interactions functioning in daily-life, a domain still little studied.

However, results of the present study should be considered in light of several methodological limitations. First, EMA relies on participants subjective self-report. Although one member of the research team went over EMA items with all the participants, interpretation may still differ from one individual to another. Moreover, as the 22q11DS group had a significantly lower IQ than both ASD and HC, the level of comprehension could have been different between the groups. Of note, Wilson and al. (35) validated EMA feasibility in a population with moderate intellectual disability but this technique had rarely been used in 22q11DS population (39,40). This is why we took time to go through the protocol with each participant and to carefully read and explain each item, as well as closely monitoring them during the full EMA period. Being available for questions and technical issues experimented by participants also had an impact on study compliance, since only 5 participants were excluded from the original sample because of an insufficient number of answered beeps.

Secondly, heterogeneity within the 22q11DS and ASD groups should be considered. Indeed, various comorbidities and medications were present in both clinical groups, possibly having an impact on the results. However, comorbidities are more the rule than the exception in neurodevelopmental disorders (e.g., 106,107). Given the variety of comorbidities reported, it wasn't possible to subdivide our groups accordingly but future studies should aim to further investigate this important question. Six participants with 22q11DS scored above the clinical cutoff on the SCQ, suggesting concerns for a potential diagnosis of ASD (the presence of an ASD diagnosis was not formally examined in this group). To examine the influence of these participants on the obtained results, all the analyses were conducted while excluding these participants and the results remaining unchanged. This suggests that the results obtained in the 22q11DS group are not explained by the presence of comorbid autistic traits in a subgroup of participants. Another limitation of the current study is that only 8% of the ASD group presented low intellectual functioning. For this reason, the obtained results cannot be extended to the low functioning part of the spectrum. However, contrary to previous research in ASD using EMA (35,42–44,46,47), not

only high functioning individuals were recruited. Finally, alexithymia wasn't examined in the present study. Given the high prevalence of alexithymia among individuals with ASD (108), it would have been useful to get a deeper comprehension on how this could influence their answers.

Conclusions

The present study showed comparable *social behaviors* in ASD and 22q11DS, with an increased percentage of time spent with people they live with and less time spent with familiar people than HC. However, the two clinical groups did not differ from HC on the amount of time spent alone, challenging the commonly accepted assumption that neurodevelopmental disorders are characterized by social withdrawal. Regarding *social experiences*, the results of the present study point towards distinctive social phenotypes in ASD and 22q11DS, with a more negative experience of social interactions and greater loneliness in individuals with ASD, and a more positive experience of social interactions among individuals with 22q11DS. Therefore, even if adolescents and young adults with ASD and 22q11DS individuals are similar from a quantitative perspective (*i.e.* social behaviors), they differ from each other on a qualitative view (*i.e.* social experiences), which emphasizes the need to develop specific intervention targets in the two populations.

Declarations

Ethics approval and consent to participate

This study was approved by the Swiss Ethics Committee on research involving humans (Commission Cantonale d'Ethique de la Recherche sur l'Etre Humain – CCER) in Geneva (CH). Written consent was asked from caregivers for all participants with ASD and 22q11DS, as well as for HC under 18 years.

Consent for publication

Not applicable

Availability of data and material

The data set is publicly available through the YARETA data preservation system.

Competing interest

The authors declare that they have no competing interests.

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Author Contributions

MS designed the EMA protocol. CF and LI collected the data and supervised participants during data collection. MS contributed to the statistical analyses. CF conducted the statistical analyses and wrote the first draft of the manuscript. MS provided critical revisions. All the co-authors commented on the manuscript and approved its submission.

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Abbreviations

22q11DS: 22q11.2 deletion syndrome

ASD: autism spectrum disorders

HC: healthy controls

ExpA: experience of aloneness

ExpSI: experience of social interactions

EMA: Ecological Momentary Assessment

PA: positive affect

NA: negative affect

CCER: Commission Cantonale d'Ethique de la Recherche sur l'Etre Humain

ADI-R: Autism Diagnostic Interview-Revised

ADOS-2: Autism Diagnostic Observation Schedule, second version

SCQ: Social Communication Questionnaire

WAIS-IV : Wechsler Adult Intelligence Scale, fourth edition

WISC-V : Wechsler Intelligence Scale for Children, fifth edition

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Tables

Tables 1-3 are available as downloads in the Supplementary Files section.

Supplementary Files

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- Table1samplecharacteristics.xlsx
- Table2ESMitems.xlsx
- Table3.ESMdescriptivevalue.xlsx