Social Visual Attentional Engagement and Memory in Phelan-McDermid Syndrome and Autism
Spectrum Disorder: An Eye-Tracking Study

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Abstract

The current study used eye tracking to investigate attention and recognition memory in Phelan-McDermid syndrome (PMS), a rare genetic disorder characterized by intellectual disability, motor delays, and a high likelihood of comorbid autism spectrum disorder (ASD). Social deficits represent a core feature of ASD, including decreased propensity to orient to or show preference for social stimuli. Here, we used a visual paired comparison task with both social and non-social images, assessing looking behavior to a novel image versus a previously-viewed familiar image to characterize social attention and recognition memory in PMS (n=27), idiopathic ASD (iASD, n=46), and typically-developing controls (n=29). On measures of attention, all groups spent a similar amount of time viewing the images; however, the rate of looking back-and-forth between images was lowest in iASD. Furthermore, while all groups demonstrated recognition memory when novel stimuli were initially presented, participants with PMS showed the weakest novelty preference compared to controls. Finally, the iASD, but not PMS, group showed enhanced novelty preference for non-social stimuli. Across indices, individuals with PMS and ASD performed more similarly to PMS without ASD and less similarly to the iASD group. These findings provide further evidence of differences in attention and memory for social stimuli in ASD and contrasts idiopathic autism with PMS.

Lay summary: Difficulty understanding social information is a core problem in autism. Here, we measure attention and memory for social images in groups of individuals with Phelan-McDermid syndrome (the most frequent single-gene cause of autism), autism without known genetic cause, and controls. We find differences among groups, extending knowledge regarding social deficits in autism with known and unknown genetic cause.

- 47 *Keywords:* visual attention, autism spectrum disorder, recognition memory, Phelan-
- 48 McDermid syndrome, social processing, eye tracking

Social Visual Attentional Engagement and Memory in Phelan-McDermid Syndrome and Autism Spectrum Disorder: An Eye-Tracking Study

Phelan-McDermid syndrome (PMS) is a rare developmental disorder that is characterized by broad cognitive delays, delayed or absent speech, and hypotonia (Phelan, 2008; Phelan & McDermid, 2011). Caused by a deletion or mutation in the chromosome region 22q13.3, disruption of the *SHANK3* gene causes the behavioral phenotype of the disorder (Sarasua et al., 2014; Harony-Nicolas et al., 2015), with larger deletion sizes correlating with increased symptom severity (Soorya et al., 2013; Sarasua et al., 2011). In animal models, deficient *Shank3* expression results in atypical cognitive processes that include impaired visual discrimination and memory (Kouser et al., 2013; Copping et al., 2017) and diminished expressive communication (Berg et al., 2018; Bozdagi et al., 2010; Wang et al., 2011), yet intact social approach behaviors (Copping et al., 2017; Drapeau et al., 2018). Many of these features are also seen in the clinical phenotype. Indeed, individuals with PMS show persistent communication deficits (Zwanenburg et al., 2016; Oberman et al., 2015). A majority have minimal or absent speech (Phelan et al., 2001; Rankine et al., 2017), with intellectual disabilities (ID) reported in most cases (Soorya et al., 2013; De Rubeis et al., 2018). Additional behavioral characteristics include sleep disturbances, impulsivity, and inattention (Costales & Kolevzon, 2015; Richards et al., 2017; Laura et al., 2018; De Rubeis et al., 2018). In a subset of individual with PMS having point mutations, De Rubeis et al. (2018) reported that up to 65% are hyperactive, with broad attentional problems.

Studies have reported a high prevalence of autism spectrum disorder (ASD) diagnoses among individuals with PMS (Soorya et al., 2014; Manning et al., 2004); in fact, loss of functioning of *SHANK3* is the most frequent single-gene cause of ASD and ID (Leblond et al.,

2014; Betancur & Buxbaum, 2013). ASD is characterized by social and communication deficits as well as restricted interests and repetitive behaviors (American Psychiatric Association, 2013). Within the social domain, these impairments include poorly modulated eye contact, a diminished awareness and understanding of the thoughts and intention of others, and difficulties in social engagement (Tager-Flusberg, 2010). In comparison to idiopathic ASD (iASD), a lower proportion of individuals with PMS have impairments in social approach and engagement behaviors, although these children struggle with directing attention more than those with iASD (Richards et al., 2017). While social deficits are prominent in both iASD and PMS, it remains unclear how deficits in specific social behaviors converge or diverge between these two clinical groups.

It has been suggested that the behavioral manifestations of social dysfunction in ASD are the consequence of atypical attentional processing (Chita-Tegmark, 2016). Typically developing infants display a sensitivity to social cues in their environment (Striano & Reid, 1999), and an attentional predisposition towards social stimuli is helpful for effective communication and language acquisition (Csibra & Gergely, 2009). Individuals with ASD, however, fail to orient to social stimuli (Dawson et al., 2004) and also show an absence of preferential attention (Klin et al., 2009) and impaired recognition (Bradshaw, Shic, & Chawarska, 2011) particular to social input. In a visual paired comparison task that tested visual memory by pairing an unfamiliar stimulus with a familiar one, toddlers with ASD showed differential eye gaze patterns and reduced recognition memory for social stimuli compared to typically developing controls (Chawarska & Shic, 2009). Here, preferential looking towards the novel stimuli infers recognition memory of the familiar stimulus (Fagan, 1970). Orienting to non-social stimuli, on the other hand, appears intact in ASD (Dawson et al., 2004). Together, these results reveal a

reliable pattern of atypical attentional and memory processes for social information in iASD. However, it is unknown whether a similar pattern of visual attention and memory impairments specific to social stimuli is also present in PMS.

The goal of the present study was to examine processing of social stimuli in PMS, in comparison to iASD and typically developing (TD) controls, using a visual paired comparison task to reveal syndrome-specific attentional and memory processing deficits of social information. We hypothesized, consistent with previous literature, that social attention and memory in iASD is atypical such that novelty preference for social stimuli would be reduced in comparison to non-social stimuli. We further expected that, relative to the iASD group, individuals with PMS would have a global deficit in memory and attention that was less specific to social recognition memory and more consistent with broad attentional challenges.

Method

Participants

Eye tracking data were collected from two- to 37-year-old children and adults with iASD ($n=46$), PMS ($n=27$), and TD ($n=29$). Age and sex distributions for each group are reported in Table 1. Participants were excluded if they lacked sufficient data, such as not completing a minimum of one social and one non-social trial type (no eye gaze data during *familiarization* or *test*), or had an average proportion looking during *familiarization* below 0.25, indicating that they were attending to the images less than 25% of the total viewing time. Legal guardians gave consent and assent was obtained from participants when appropriate. Procedures were approved by the Program for the Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai.

For the iASD and PMS groups, clinical diagnosis was confirmed with the Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2012) and the Autism Diagnostic Interview-Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994), followed by clinical consensus among licensed clinical psychologists and psychiatrists. All individuals in the iASD group met DSM-5 (American Psychiatric Association, 2013) criteria for ASD; in the PMS group, 16 participants met criteria for ASD, (59%). For the PMS group, chromosomal microarray or targeted sequencing was conducted to verify genetic diagnosis. Pathogenic deletion or mutation of the *SHANK3* gene was necessary and sufficient for a PMS diagnosis.

All participants in the iASD and PMS groups were administered standardized measures of intellectual or developmental functioning. Depending on age and functioning level, participants received one of the following tests: the Stanford-Binet Intelligence Scales (SB-5; Roid, 2003), the Wechsler Intelligence Scale for Children (WISC-V; Wechsler, 2014), the Wechsler Abbreviated Scale of Intelligence (WASI-II; Weschler, 2011), the Differential Ability Scales (DAS, DAS-II; Elliot, 2007), or the Mullen Scales of Early Learning (Mullen, 1995). Developmental quotients [DQ: (mental age / chronological age * 100)] scores were computed from subtest-level age equivalent scores in order to combine data across the different IQ tests administered. Table 1 shows a summary of assessment scores.

Apparatus and Testing Procedure

An EyeLink 1000 plus eye-tracker in head-free mode with a 17-inch LCD monitor and 1280 × 1024 pixel at 32 bits per color display, with a refresh rate of 60 Hz was used for data collection. Data were acquired at 500 Hz with a 5- or 13-point calibration used on each participant before the start of the task.

Testing was performed in a dark, quiet room. Participants were positioned at a small table in either a chair or a booster seat roughly 50 cm from the eye tracker and monitor. Ambient sound and light were minimized in order to reduce distraction and tracking interference. The experimenter would give generic verbal instructions: “Look at the images you see on the screen. Between each set of images, look at a dot in the center of the screen.” Importantly, comprehension of these instructions was non-critical; participants were allowed to passively view on-screen images, and the trials were presented only when participants were fixating the screen (see below). In this way, the task was accessible to individuals with a wide range of cognitive and language abilities.

Stimuli and Experimental Procedure

The visual stimuli, from Rose et al. (2013), comprised of achromatic faces (social) and multicolored abstract patterns (non-social) (see Figure 1A), on a black background. At a viewing distance of 50 cm, stimuli subtended a $14.2^{\circ} \times 10.2^{\circ}$ visual angle. The task was presented using the EyeLink Experiment Builder software application.

This study used the well-established visual paired comparison paradigm (Fagan, 1990; Rose et al., 2013). Trials began with a *familiarization* period. During this phase, identical images were presented in pairs, one image on the left and one on the right of the vertical meridian. As per Rose et al. (2013), viewing times were 10 sec (social images) or 5 sec (non-social images), excluding the time when the participant’s eye gaze left the display monitor. Next, during the *test* period, the image displayed during familiarization was paired with a novel image for 5 sec (pre-switch), after which the two images switched sides and were displayed for an additional 5 sec (post-switch) (Figure 1B). The location of the novel stimulus was balanced across stimulus types

and test periods. As per Rose et al. (2013), participants viewed nine trials in total: five social and four non-social. Order of social and non-social trials was fixed and alternated between the two trial types. A flashing target and a loud “spaceship” noise was shown for a few seconds between each trial to ensure participants returned to a central, neutral fixation point. The experimenter would visually confirm the position of the participant’s eye gaze before manually initiating the start of each trial.

Data analysis

Areas of interest (AOI) were defined as the rectangular area encompassing the image (AOI size: $14.2^{\circ} \times 10.2^{\circ}$ of visual angle). Participants completed an average of 8.90 ± 0.07 (Mean, SE) trials (iASD: 8.83 ± 0.15 ; TD: 8.97 ± 0.03 ; PMS: 8.96 ± 0.37) with no significant differences between groups, $F_{2,101} = 0.47$, $p = 0.63$, $\eta_p^2 = 0.009$.

In *familiarization*, total visit duration (TVD) in AOIs, corrected for total display time difference of stimulus type, was calculated for both the left and right image, then summed to determine the proportion of total image exploration time. The data were subjected to a 2×3 repeated measures analysis of variance (ANOVA) with stimulus type (social, non-social) as the within-subjects factor and diagnosis (iASD, PMS, TD) as the between subject factor. In addition, a rate of entering the AOI established the amount of switching back and forth between the two identical images and was analyzed with $2 \times 2 \times 3$ repeated measures ANOVA with stimulus type, location (left, right) and diagnosis as levels of the independent variable (IV). The rate was calculated using the number of entries into the AOI divided by the exposure time (social: 10sec; non-social: 5 sec).

During *test*, total visit duration for each image (novel and familiar) was calculated separately for the initial 5 sec presentation (pre-switch) and after the images switched sides

(post-switch). A preference score was calculated as the average time spent on the AOI for the familiar image subtracted from the time spent on the novel image divided by the sum of time spent on either image: $(novel - familiar)/(novel + familiar)$. A score significantly different from zero in either direction (positive for novelty or negative for familiarity) was indicative of recognition memory. Preference scores were subjected to a $2 \times 2 \times 3$ repeated measures ANOVA with stimulus type, switch period (pre-, post-), and diagnosis as IV levels. One sample t-tests were conducted separately for each clinical group to analyze the existence of a preference (i.e., significant difference from zero/no preference, where equal time is spent on the familiar and novel images).

All tests were Bonferroni corrected with a two-tailed 0.05 significance criterion.

Results

Clinical and Demographics Measures

The final sample showed no significant difference among groups for age, $F_{2,101}=0.16$, $p=0.85$, $\eta_p^2=0.003$. There was a significant difference in DQ, $F_{2,30.31}=45.17$, $p<0.001$, $\eta_p^2=0.57$, with eighteen participants missing DQ scores (ASD: 5; PMS: 0; TD: 9). The DQ scores of the TD group (144.89 ± 14.07) were higher than both the iASD ($90.62 \pm .46$, $p = 0.003$ Games-Howell) and PMS (23.65 ± 3.27 , $p < 0.001$ Games-Howell) groups. The iASD group also had significantly higher DQ scores compared to the PMS group ($p < 0.001$ Games-Howell). A significant sex difference was also found among the groups, $\chi(2)=13.84$, $p=0.001$. A post-hoc Mann-Whitney test revealed the iASD group had a greater proportion of males when compared with the PMS ($p=0.012$) and TD ($p=0.003$) groups. This is consistent with male:female ratio in ASD (Baio et al., 2018). No other comparisons for sex ratio were found to be significant (TD/PMS: $p=1.00$).

Familiarization

Attention to social and non-social stimuli was compared among groups during the *familiarization* period. There was no significant main effect of stimulus type ($F_{1,99}=0.45, p=0.50, \eta_p^2 = 0.005$) or diagnostic group ($F_{2,99}=2.97, p=0.056, \eta_p^2 = 0.06$), and no significant stimulus by diagnosis interaction ($F_{2,99}=0.52, p=0.60, \eta_p^2 = 0.01$) on measures of proportion looking time.

This finding indicates similar attention to social and non-social stimuli across groups (Figure 2A).

To investigate differences in looking patterns, we analyzed the rate of saccade entries into the left and right images. We found a significant main effect for stimulus type ($F_{1,99}=41.86, p<0.001, \eta_p^2 = 0.30$). Across all groups, participants had a higher rate of AOI entries to non-social stimuli (0.52 ± 0.02) than social stimuli (0.44 ± 0.01). There was no significant main effect of image location, i.e. left versus right image ($F_{1,99}=0.15, p=0.70, \eta_p^2 = 0.001$). However, a statistically significant main effect of group ($F_{2,99}=6.19, p=0.003, \eta_p^2 = 0.11$) was detected wherein, overall, the iASD group made fewer entries into the AOI (0.42 ± 0.02) compared with the PMS group ($0.53\pm0.03; p = 0.003$). No other comparisons with the TD group (0.49 ± 0.03) were found to be significant (TD/iASD: $p=0.13$; TD/PMS: $p=0.62$).

A significant group $\times$ stimulus type interaction ($F_{1,99}=10.51, p<0.001, \eta_p^2 = 0.18$) was also detected. Follow-up one sample t-tests examining the AOI entry rate difference between non-social and social images (non-social – social) revealed that the TD group showed the largest difference in AOI entry rate between social and non-social (mean difference: $0.17\pm0.02; p < 0.001$) stimuli favoring non-social images, followed by the iASD group ($0.05\pm0.02; p = 0.005$). The PMS group showed no significant difference between entry rate between stimulus types

(0.03 ± 0.03 ; $p = 0.99$). No other interactions were significant (group $\times$ location: $F_{2,99}=0.40$, $p=0.67$, $\eta_p^2 = 0.01$; stimulus type $\times$ location: $F_{1,99}=3.79$, $p=0.054$, $\eta_p^2 = 0.04$; group $\times$ stimulus type $\times$ location: $F_{2,99}=0.31$, $p=0.74$, $\eta_p^2 = 0.006$), (Figure 2B). In sum, engagement with stimuli differed among the groups in looking pattern by stimulus type but not overall time on screen.

Test

The *test* period introduced a novel image, evaluating memory through preference for the social and non-social stimuli. We found a significant main effect of test period (pre-/post-switch: $F_{1,99}=200.41$, $p<0.001$, $\eta_p^2 = 0.67$). Across groups, participants looked less at the novel image during the post-switch period (-0.12 ± 0.02) compared with the pre-switch test period (0.40 ± 0.02). There was no main effect of stimulus type ($F_{1,99}=0.18$, $p=0.068$, $\eta_p^2 = 0.002$). Participants spent the same proportion of time looking at the non-social novel image (0.13 ± 0.02) as the social novel image (0.13 ± 0.02). There was no significant main effect of group ($F_{2,99}=0.75$, $p=0.48$, $\eta_p^2 = 0.02$). The PMS group spent the same proportion of time looking at the novel images (0.11 ± 0.02) compared to the TD (0.15 ± 0.02 , $p=0.67$) and iASD (0.14 ± 0.02 , $p=1.00$) groups, and TD and iASD groups also did not differ in their preference score ($p=1.00$). The interactions between test period $\times$ group ($F_{2,99}=4.43$, $p=0.01$, $\eta_p^2 = 0.08$) and test period $\times$ stimulus type ($F_{1,99}=24.98$, $p<0.00$, $\eta_p^2 = 0.20$) were found to be significant, and are unpacked below. There were no other significant interactions (stimulus type $\times$ group: $F_{2,99}=1.52$, $p=0.22$, $\eta_p^2 = 0.03$; test period $\times$ stimulus type $\times$ group: $F_{2,99}=0.20$, $p=0.82$, $\eta_p^2 = 0.004$).

To further parse the main effect and interactions of test period, we analyzed pre- and post-switch separately. In the pre-switch period, we found a main effect of group ($F_{2,99}=4.94$,

$p=0.009$, $\eta_p^2 = 0.09$). The PMS group had a significantly smaller novelty preference (0.30 ± 0.04) compared to the TD group (0.48 ± 0.04 ; $p = 0.007$). The iASD group had more intermediate novelty preference (0.41 ± 0.03) and did not differ from either group (PMS: $p = 0.10$; TD: $p = 0.57$). There was no significant group by stimulus type interaction ($F_{2,99}=0.88$, $p=0.42$, $\eta_p^2 = 0.02$). However, the main effect of stimulus type was significant ($F_{1,99}=11.84$, $p=0.001$, $\eta_p^2 = 0.12$), with stronger novelty preference observed for non-social stimuli (0.45 ± 0.03) compared with social stimuli (0.34 ± 0.03) across groups. It is notable that one-sample t-tests exposed that this difference in magnitude between non-social and social preference scores was driven by the iASD group (mean difference = 0.16 ± 0.05 ; $p=0.005$), whereas differences by stimulus type were much more subtle in PMS (0.08 ± 0.06 ; $p=0.56$) and TD (0.08 ± 0.05 ; $p=0.37$). In aggregate, these results identify differences between groups in their recognition memory, notably the iASD group displayed a stronger novelty preference for non-social stimuli while the PMS group did not exhibit a stimulus preference as strongly when compared with controls.

For the post-switch period, the main effect of group ($F_{1,99}=1.80$, $p=0.17$, $\eta_p^2 = 0.04$) was no longer significant. The iASD group showed a similar preference (-0.14 ± 0.03) compared with the PMS group (-0.06 ± 0.04 , $p = 0.51$), and the TD group (-0.18 ± 0.04) did not differ from either the iASD ($p=1.00$) or the PMS group ($p=0.20$). A significant main effect of stimulus type ($F_{1,99}=16.99$, $p<0.001$, $\eta_p^2 = 0.15$) revealed that there was a stronger familiarity preference for non-social stimuli (-0.19 ± 0.03) compared to social (-0.07 ± 0.03) in the post-switch periods. There was no significant interaction ($F_{1,99}=0.65$, $p=0.53$, $\eta_p^2 = 0.01$) in the post-switch test.

Finally, to test for the presence of a novelty/familiarity preference for each group and stimulus type, we ran 12 one-sample t-test, Bonferroni corrected (Figure 3). It was found that the

TD group had a novelty preference in the pre-switch test for both stimulus types (non-social: 0.51 ± 0.05 , $p < 0.001$; social: 0.44 ± 0.04 , $p < 0.001$). During the post-switch period, controls demonstrated a familiarity preference for non-social stimuli (-0.27 ± 0.05 , $p < 0.001$), but neither novelty nor familiarity preference for social stimuli (-0.09 ± 0.04 , $p = 0.50$). Similar to the TD group, the iASD group showed a novelty preference pre-switch (non-social: 0.49 ± 0.04 ; $p < 0.001$; social: 0.32 ± 0.04 , $p < 0.001$) and a familiarity preference post-switch for non-social stimuli (-0.26 ± 0.05 ; $p < 0.001$), but no preference for social stimuli (-0.09 ± 0.04 , $p = 0.31$). The PMS group had a novelty preference during the pre-switch period (social: 0.26 ± 0.05 , $p < 0.001$; non-social: 0.34 ± 0.05 , $p < 0.001$), but neither familiarity nor novelty preference during the post-switch period (social: -0.01 ± 0.05 , $p = 1.00$; non-social: -0.12 ± 0.05 , $p = 0.23$). This last finding suggests decay of memory in PMS by the post-switch interval.

ASD Diagnosis in PMS

The PMS group was further divided into participants with a co-morbid ASD diagnosis (PMS⁺; $n=16$; females: 9 (56%)) and those without an ASD diagnosis (PMS⁻; $n=11$; females: 5 (45%)). There were no significant differences in DQ ($t_{25}=1.05$, $p=0.30$; PMS⁺: 20.81 ± 3.92 , PMS⁻: 27.78 ± 5.62) or age, $F_{1,26}=1.85$, $p=0.18$, $\eta_p^2 = 0.07$ (PMS⁺: 9.51 ± 1.53 years; PMS⁻: 12.79 ± 1.85 years). The separate PMS groups were compared to the iASD and TD groups and subjected to the same analyses of attentional engagement (proportion looking and AOI entry rate) and recognition memory (preference scores) as in the primary analyses.

During *familiarization*, as with earlier group analysis, there were no significant differences in proportion looking time among groups ($F_{3,98}=2.20$, $p=0.09$, $\eta_p^2 = 0.06$) or between stimulus types ($F_{1,98}=0.48$, $p=0.49$, $\eta_p^2 < 0.005$), and there was no significant group by stimulus

type interaction e ($F_{3,98}=0.37, p=0.77, \eta_p^2 = 0.01$). On measures of looking patterns, the main effect of stimulus type was still significant ($F_{1,98}=21.34, p<0.001, \eta_p^2 = 0.2$). There was also a main effect of group ($F_{3,98}=4.18, p=0.008, \eta_p^2 = 0.14$) such that the PMS^+ group (0.54 ± 0.03) had a higher overall AOI entry rate than the iASD group ($0.42\pm0.02; p=0.014$). No other comparisons reached significance (iASD/ PMS^- : $p=0.23$; iASD/TD: $p=0.26$; PMS^+ / PMS^- : $p=1.00$; TD/ PMS^- : $p=1.00$; TD/ PMS^+ : $p=1.00$). In addition, the interaction effect was significant (stimulus type $\times$ group: $F_{3,98}=7.78, p<0.001, \eta_p^2 = 0.19$) where further post-hoc analyses with a one-way ANOVA and paired t-tests found that the TD group showed a significant difference in AOI entry rate between social and non-social stimuli (mean difference = 0.17 ± 0.02) compared to the iASD ($0.05\pm0.02, p=0.001$), PMS^+ ($0.06\pm0.03, p=0.035$), and the PMS^- ($-0.013\pm0.04, p=0.001$) groups. No other comparisons were significant (iASD/ PMS^- : $p=0.79$; iASD/ PMS^+ : $p=1.00$; PMS^- / PMS^+ : $p=0.90$).

During *test*, as with earlier analyses, there was a significant effect of test period, $F_{1,98}=137.30, p<0.001, \eta_p^2 = 0.6$, with higher novelty preference during pre- than post-switch. The main effect of stimulus type ($F_{1,98}=0.27, p=0.61, \eta_p^2 = 0.003$) and group ($F_{3,98}=0.91, p=0.44, \eta_p^2 = 0.03$) were found not to be significant, and significant interaction effects remained (test $\times$ group: $F_{3,98}=3.07, p=0.031, \eta_p^2 = 0.09$; test $\times$ stimulus type: $F_{1,98}=17.81, p<0.001, \eta_p^2 = 0.15$). No other interaction effects reached statistical significance (stimulus type $\times$ group: $F_{3,98}=1.07, p=0.37, \eta_p^2 = 0.03$; test $\times$ stimulus type $\times$ group: $F_{3,98}=0.13, p=0.94, \eta_p^2 = 0.004$).

Dissecting the pre-/post- switch further, the switch periods were again analyzed separately. During the pre-switch period, there was a main effect of stimulus type ($F_{1,98}=7.85,$

$p=0.006$, $\eta_p^2 = 0.07$), with a stronger novelty preference found for non-social (0.42 ± 0.03) compared with social (0.33 ± 0.03) stimuli across groups. Replicating previous analyses of the difference score between non-social and social preference (non-social – social), applying one-sample t-tests, there were no differences in either the PMS⁺ (mean difference = 0.093 ± 0.073 ; $p=0.28$) or PMS⁻ (mean difference = 0.060 ± 0.099 ; $p=1.00$) groups. There was again a main effect of group ($F_{3,98}=3.72$, $p=0.014$, $\eta_p^2 = 0.10$). Here, we clarify that, across stimulus types, the TD participants show a stronger preference score than the PMS⁺ group (0.26 ± 0.05 ; $p=0.009$), whereas the preference score for the PMS⁻ group (0.35 ± 0.65) did not differ from the other groups (TD: $p=0.65$; iASD: $p=1.00$; PMS⁺: $p=1.00$). The interaction effect was not significant ($F_{3,98}=0.60$, $p=0.61$, $\eta_p^2 = 0.02$). As in the main analyses, during post-switch there was a significant effect of stimulus type ($F_{1,98}=12.89$, $p=0.001$, $\eta_p^2 = 0.12$) such that there was a greater familiarity preference for the non-social stimuli (-1.78 ± 0.3) than social (-0.052 ± 0.03). No other effects were significant (group: $F_{3,98}=1.19$, $p=0.32$, $\eta_p^2 = 0.04$; stimulus type $\times$ group: $F_{1,98}=0.46$, $p=0.71$, $\eta_p^2 = 0.01$)

One-sample t-test revealed that the PMS⁻ group had a significant novelty preference for both stimulus types during the pre-switch period (social: $p=0.002$; non-social: $p=0.006$), whereas they showed no preference during post-switch (social: $p=1.00$; post-switch non-social: $p=1.00$). The PMS⁺ group, showed a similar pattern, with a novelty preference during both social and non-social pre-switch intervals (social: $p=0.005$; non-social: $p<0.001$), but not during the post-switch period (social: $p=1.00$; non-social: $p=1.00$) (Figure 3).

Discussion

The present study in Phelan-McDermid syndrome examined two aspects of cognition that have been implicated in ASD: social attentional engagement and memory. Each has been proposed as a causal factor underlying core impairments in ASD (Dawson, Webb, McPartland, 2005), although this represents the first study to examine these constructs in PMS, one of the most common single-gene causes of ASD. We found that attentional engagement did not differ among iASD, PMS, and TD groups for social or non-social images. However, the groups were dissociable in their looking patterns and preferential looking behavior towards novel versus familiar images. In particular, participants with iASD showed less active looking during stimulus familiarization compared to those with PMS and, interestingly, in particular those PMS participants with ASD. Novelty preference during the pre-switch test phase, in which novel stimuli were first presented, was weakest in PMS, and particularly so in those with PMS who met criteria for ASD. Finally, while all groups showed a greater novelty preference for non-social (versus social) stimuli during the pre-switch test period, further inspection revealed that participants with iASD were the main drivers of this effect, showing a strong bias in their novelty preference for non-social stimuli. This effect was not, however, seen in individuals with PMS and ASD.

Our results in iASD generally are consistent with prior studies that report atypical processing of social stimuli in ASD. Namely, the novelty preference in the ASD group was considerably lower on trials with social images than on non-social ones. A recent meta-analysis indicated that individuals with ASD are worse at remembering and discriminating facial identity (Weigelt, Koldewyn, Kanwisher, 2012), which is consistent with our findings. Some have attributed this domain-specific impairment for faces to reduced reward placed on social information (Chevallier et al., 2012). Other research suggests that the complexity of faces

presents a challenge for individuals with ASD in terms of discerning relevant and irrelevant information features, thereby affecting memory processes (Van de Cruys et al. 2014).

During test (pre-switch), all groups demonstrated a novelty preference, indicating that participants were able to discriminate between the familiar and unfamiliar items. However, this preference was significantly weaker in PMS when compared with the TD controls. Moreover, during post-switch, the PMS group showed neither novelty nor familiarization, suggesting recognition memory had decayed over the 5 sec pre-switch test period in PMS, whereas it remained intact for the TD and iASD groups. These results are in consistent studies of *Shank3*-deficient mice revealing specific deficits in the mediation of glutamate expression (Bozdagi et al, 2010), a neurotransmitter involved in learning and memory through long-term potentiation (McEntee & Crook, 1993).

Interestingly, reduced overall novelty preference in PMS during the pre-test interval was driven by the subset of PMS participants who have co-morbid ASD, though this reduced overall novelty preference was not observed in iASD. Additionally, though individuals with iASD showed a stronger novelty-preference for non-social stimuli, this effect was not observed for ASD associated with PMS. Participants with PMS and ASD looked more similar to participants with PMS without ASD and to controls, showing a novelty preference regardless of stimulus type. These findings suggest that social/non-social memory and novelty preference looks different in those with ASD caused by PMS relative to the profile observed in iASD more generally.

We found comparable viewing times among iASD, PMS, and TD groups when participants were initially presented with identical image pairs during the familiarization phase. The lack of any differences suggests that each group had equitable cumulative looking times to

become familiar with the images, which further suggests that differences in novelty preference were not due to differences in familiarity or attention. However, across groups, there were some notable differences in rates of looking away and returning to the image. This type of eye gaze patterns indexes initial exploration of images and may measure the process of comparing the pair of images (Rose, Feldman, & Jankowski, 2003). In iASD, there were lower rates of looking behaviors overall, but tendency for more active looking at non-social versus social images, as was observed in TD. In the PMS group, however, overall rates of looking between images was comparable to the TD group, but the difference in looking rates for social versus non-social stimuli observed in the other two groups was absent.

These results could suggest that looking behaviors, more than looking time, contribute to subsequent differences in memory and preference for social and non-social stimuli. However, previous research has suggested a high level of switching back and forth between items was correlated with better memory performance (Kovack-Lesh, Horst, Oakes, 2008); why the PMS group shows intact rates of looking switches yet poorer memory by the post-test interval could be attributed to deficient long-term potentiation, in spite of intact initial encoding behavior and early (pre-switch) memory. Overall, those individuals with PMS and co-morbid ASD had the highest rates of looking between stimuli across all four groups, whereas those with idiopathic ASD had the lowest. Here again, results highlight a pattern of dissociable social impairments in ASD associated with PMS versus idiopathic ASD more broadly.

While the switch during the test period was introduced to control for side preferences, the difference in performance (from novelty preference to familiarity preference in TD and iASD and from novelty preference to no preference in PMS) between the pre- and post-switch periods suggest that participants were not acting the same across the test periods. One interpretation of

these findings is that the abrupt change in images during the switch could be interpreted by some participants as a novelty of location. In addition, the post-switch period could be capturing a disengagement cost, or the time needed to disengage attention from an image.

Study limitations are due primarily to factors inherent in studying rare disease populations. First, groups were not matched on DQ scores. ID is characteristic of PMS; while some participants in our ASD sample had ID, the DQ scores in TD and iASD were both substantially higher than in PMS. However, the visual paired comparison paradigm has been used successfully with infants as young as 5-month-olds (Rose et al., 2001), has minimal instructions, and is free-viewing in nature. Furthermore, we found no group differences in looking time during image familiarization suggesting the PMS group were broadly attentive with their eye gaze on the display monitor. However, we cannot discount differences in DQ between PMS and other groups as a factor influencing viewing behavior. Second, our study included participants across a wide age range in order to recruit an adequate sample size. However, the rarity of this disorder emphasizes its uniqueness. Lastly, while stimuli differed across trials and between stimulus types, the images were taken from previously published studies and were calibrated for equal attractiveness within a trial (Rose et al., 2013; Rose et al. 2001); however, it remains possible that differences between calibrated stimuli across social and non-social images could impact results.

In summary, while we found no general attentional engagement impairments in iASD or PMS, there were signs of disorder and domain-specific memory impairments and looking patterns. We found that, overall, individuals with PMS show a reduced novelty preference regardless of stimulus type, whereas individuals with iASD, but not PMS, showed enhanced novelty preference for non-social relative to social stimuli. In addition, both looking behaviors

431 and novelty preference differed between iASD and ASD in the context of PMS. These unique
432 patterns of social attentional engagement and memory in PMS differentiate it from iASD and
433 could both clarify underlying mechanistic alterations and inform treatment targets for PMS. In
434 addition, searching for PMS-like attention and memory patterns could serve as a way to stratify
435 individuals within heterogeneous iASD samples and potentially apply knowledge gained in PMS
436 to these iASD subsets as well.

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Table 1: Participant demographics

	Group Means (mean, SE)			Statistics	
	iASD (n=46)	PMS (n=27)	TD (n=29)	F or χ^2	<i>p</i>
Age	10.27 (0.89)	10.85 (1.20)	11.06 (1.20)	0.16	0.85
DQ	90.62 (5.46)	23.65 (3.27)	145.89 (14.07)	45.17	< 0.001
ADOS [‡]	12.16(1.10)	17.00(1.33)	—	7.76	0.07
Sex (% female)	9 (19.6%)	14 (51.8%)	17 (58.6%)	13.84	0.001

[‡]there were missing values for 11 participants (15%), (ASD: n=8; PMS: n=3)

Figure 1. (A) Sample of social (left) and non-social (right) visual stimuli and (B) Trial schematic of visual paired comparison task showing a social trial. Familiarization was followed by a pre-switch test, which featured a novel image, and finally post-switch test when the novel and familiar images swapped sides.

Figure 2. Familiarization results. (A): proportion looking during social and non-social trial types. Right: The iASD (green), PMS (purple), and TD (grey) show comparable attentional engagement. (B): The PMS⁻ (blue) and PMS⁺ (red) subgroups show similar looking times. (C and D): Average area of interest (AOI) image entry rate for social (right) and non-social (left) trial types averaged across location. The iASD (green) had a lower AOI entry rate compared to the PMS group (C) and the PMS⁺ (D)

Figure 3. Test results. (A) top: pre-switch test period for social and non-social preference scores (green: iASD, purple: PMS, grey: TD), (B: blue: PMS⁻, red: PMS⁺) and bottom: post-switch test period. Values above zero denote a novelty preference and values below zero a familiarity preference. During the pre-switch period, all groups demonstrated a novelty preference. In the post-switch period, iASD and TD groups exhibited familiarity preference, whereas the PMS (A) and PMS subgroups (B) did not exhibit an image preference.