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Distinct and similar patterns of emotional development in adolescents and young adults

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Abstract

Adolescence is a developmental period of increased sensitivity to social emotional cues, but it is less known whether young adults demonstrate similar social emotional sensitivity. The current study tested variation in reaction times to emotional face cues during different phases of emotional development. Ex-Gaussian parameters μ , σ , and τ were computed, in addition to mean, median and standard deviation (SD) in reaction times (RT) during an emotional go/nogo-paradigm with fearful, happy, and calm facial expressions in 377 participants, 6–30 years of age. Across development, mean RT showed slowing to fearful facial expressions relative to both calm and happy facial cues, but μ revealed that this pattern was specific to adolescence. In young adulthood, increased variability to fearful expressions relative to both happy and calm ones was captured by SD and τ . The findings that adolescents had longer response latencies to fearful faces, whereas young adults demonstrated greater response variability to fearful faces, together reflect how social emotional processing continues to evolve from adolescence into early adulthood. The findings suggest that young adulthood is also a vulnerable period for processing social emotional cues that ultimately may be important to better understand why different psychopathologies emerge in early adulthood.

KEYWORDS

adolescence, emotional development, ex-Gaussian, reaction time, variability, young adulthood

1 | INTRODUCTION

Adolescence has been characterized by a heightened reactivity to social emotional cues (Casey, 2015), with teens showing greater difficulties inhibiting attention and action toward both positively and negatively valenced cues relative to children and adults (Cohen-Gilbert & Thomas, 2013; Dreyfuss et al., 2014; Grose-fifer et al., 2013; Hare et al., 2008; Heller, Cohen, Dreyfuss, & Casey, 2016;

Somerville, Hare, & Casey, 2011; Tottenham, Hare, & Casey, 2011). Recent work suggests that the development of social emotional processes extends beyond traditional definitions of adolescence (approximately 13–17 years). Young adults, 18–21 years of age, also show reduced self-control to negative social emotional cues relative to older adults (Cohen et al., 2016), suggesting protracted emotional development into young adulthood. Previous social emotional studies across development have largely focused on mean differences

*Dienke J. Bos and Michael Dreyfuss are shared first authors

[Corrections added on January 23, 2020 after first online publication: The text "Dienke J. Bos and Michael Dreyfuss are shared first authors" has been added as a footnote.]

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in performance accuracy. However, intra-individual differences in reaction times (RT) may provide an additional level of explanation that mean differences in performance do not capture (MacDonald, Nyberg, & Bäckman, 2006) and have been suggested to be a more sensitive marker of neural development (Tamnes, Fjell, Westlye, Ostby, & Walhovd, 2012). The goal of the present study is to focus on RTs with a comprehensive approach using both measures of central tendency and ex-Gaussian parameters to determine whether processing of social emotional cues is similar or distinct during adolescence/early adulthood compared to childhood and adulthood.

Reaction times are typically examined using measures of central tendency, such as mean and median, and variability, such as standard deviation (SD). Mean reaction times are thought to be an indicator of processing speed and relate to working memory capacity and intelligence during simple reaction time tasks (Deary, Der, & Ford, 2001; Fry & Hale, 1996; Larson & Alderton, 1990; Ratcliff, Schmiedek, & McKoon, 2008; Schmiedek, Oberauer, Wilhelm, Süß, & Wittmann, 2007). These cognitive processes have been shown to differ under varying emotional conditions. For example, using emotional flanker- and go-nogo paradigms, it has been shown that there is a slowing in RTs toward negatively valenced cues relative to positive ones from child- to adulthood (Grose-fifer et al., 2013; Hare et al., 2008; Tottenham et al., 2011). Longer RTs in these and other paradigms (e.g., selective attention tasks) have been suggested to reflect increased attentional capture or interference by negatively valenced cues (Grose-fifer et al., 2013; Monk et al., 2003).

In contrast to mean reaction times, inconsistency in response speed, an individual's variability in RT (SD), has been suggested to convey additional information about the efficiency of attentional resources (Bellgrove, Hester, & Garavan, 2004; Johnson et al., 2015; MacDonald, Li, & Bäckman, 2009; Stuss, Murphy, Binns, & Alexander, 2003). There is neurobiological evidence that during development reduced RT variability is reflective of brain maturation (Tamnes et al., 2012) and increased flexibility in cognitive processing (Garrett, Kovacevic, McIntosh, & Grady, 2011; McIntosh, Kovacevic, & Itier, 2008). In response to neutral, non-social cues, RT variability has been observed to change from childhood to old age following an inverted U-shape, where young adults show decreased variability relative to children and older adults (Fagot et al., 2018; Li et al., 2004; Williams, Hultsch, Strauss, Hunter, & Tannock, 2005). However, it is unknown whether RT variability is influenced by developmental differences in processing of negative and/or positive social emotional information in healthy adolescents and young adults. Such knowledge may provide deeper insight on developmental differences in social emotional processing.

Ex-Gaussian decomposition of RT distributions is a method that may meaningfully capture distinct elements of the RT distribution that are not explicitly captured by mean, median, and SD RT (Ratcliff, 1979, 1993; Whelan, 2008). *Mu* and *sigma* reflect the mean and standard deviation of the Gaussian component of the RT distribution, that is, those RTs that fall within a normal distribution of responses. *Tau* reflects the tail of the exponential distribution, which captures infrequent, slow responses. Thus, *tau* is uniquely able to represent longer RTs that are not separated out from the central tendency measures of mean and SD RT.

It has been suggested that the different ex-Gaussian parameters reflect distinct underlying cognitive processes, that are associated with different developmental trajectories (McAuley, Yap, Christ, & White, 2006; Williams et al., 2005; Williams, Strauss, Hultsch, & Hunter, 2007). Specifically, *Mu* is thought to represent processing speed, and is very similar to the cognitive processes that underlie central tendency of mean RT. In large part, the value of the ex-Gaussian approach over central tendency measurements, is to derive *sigma* and *tau*. It has been hypothesized that *sigma* reflects inconsistency in motor responsivity, whereas increased *tau* reflects attentional or inhibitory processes (Kofler et al., 2013; Schmiedek et al., 2007; Unsworth, Redick, Lakey, & Young, 2010). Evidence for changes in ex-Gaussian measures of RT in developmental populations almost exclusively comes from research in children with developmental disorders such as Attention Deficit/Hyperactivity Disorder (ADHD), where increased *tau* has been associated with attentional lapses (Buzy, Medoff, & Schweitzer, 2009; Geurts et al., 2008; Hervey et al., 2006; Karalunas, Geurts, Konrad, Bender, & Nigg, 2014; Leth-Steensen, Elbaz, & Douglas, 2000) and diagnostic differences in developmental trajectories (van Belle, Hulst, & Durston, 2015). Nevertheless, even though the exact cognitive correlates of ex-Gaussian RT measures remain elusive (Matzke & Wagenmakers, 2009), they provide distinct elements of variability in processing cues that standard metrics such as mean and standard deviation may not distinctly capture (Ratcliff, 1979, 1993).

As studies have shown that emotional brain circuitry continues to mature through early adulthood (Casey, Heller, Gee, & Cohen, 2017), we predicted that emotional valence would influence variability in response latencies to social emotional cues differentially from childhood- to young adulthood. Comparing mean, median, and SD RT with ex-Gaussian statistics, we examined RT data from participants aged 6–30 who completed an emotional go-nogo paradigm with happy, fearful, and calm faces. We chose a broad age range to make comparisons across multiple stages of development to determine whether the adolescent/early adulthood period differs compared to childhood and adulthood. Overall, we expected to observe differences in ex-Gaussian statistics of RT to emotional cues across development that would not be uncovered by mean, median, and SD RT. There is little prior work with ex-Gaussian statistics across development, but we predicted increased RT variability, captured by *sigma* and *tau*, to happy and fearful emotional facial cues, relative to calm facial cues, in adolescents and young adults—reflecting continued refinement of social emotional processing throughout adolescence and early adulthood. In addition, we predicted an adolescent-specific slowing in RTs, similar to prior work (e.g., Tottenham et al., 2011) to fearful and happy facial expressions relative to calm facial expressions.

2 | METHOD

2.1 | Participants

Data were collected from 412 healthy participants between the ages of 6 and 30, recruited from the Sackler Institute for

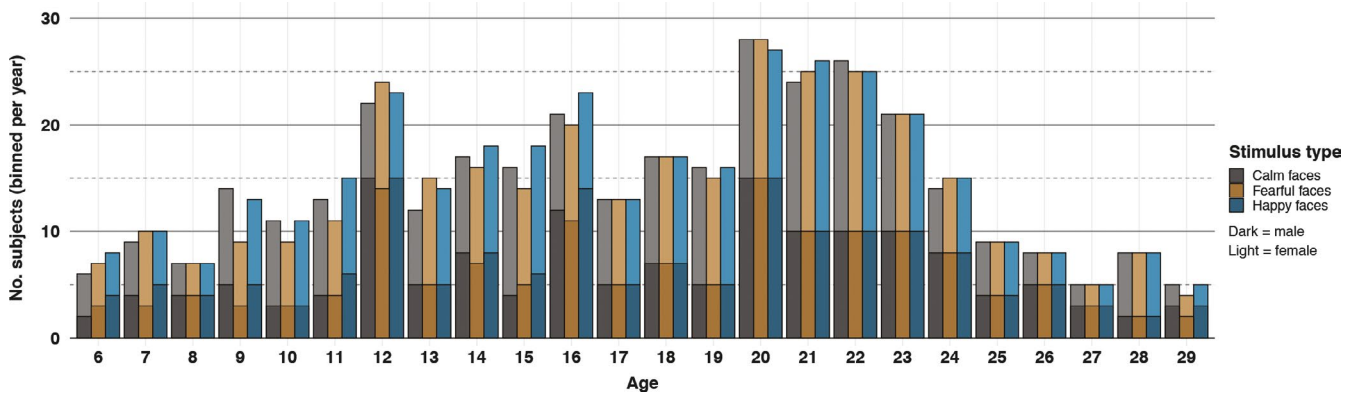


FIGURE 1 Number of participants included in the analyses displayed per year. Dark colors represent the number of males, and light colors represent the number of females included in the analyses

Developmental Psychobiology in New York, NY (169 males) (Figure 1). All participants reported no history of neurologic or psychiatric disorder and had an estimated full-scale Intelligence Quotient (IQ) above 80 (low average and above), measured by the Wechsler Abbreviated Scale of Intelligence (WASI; (Wechsler, 1999)). All participants and their parents (if minors) gave verbal and written assent and consent as approved by the Weill Cornell Medicine Institutional Review Board.

2.2 | Paradigm

The present study relied on a go-nogo paradigm with calm, happy, and fearful emotional faces, similar to other versions of this task that have been used to assess inhibitory control to social emotional stimuli (Dreyfuss et al., 2014; Hare et al., 2008; Heller et al., 2016; Somerville et al., 2011; Tottenham et al., 2011). The go/no-go paradigm generated RTs to reliably assess social emotional processing across age. Participants were instructed to press a button as fast as possible to a calm, happy, or fearful facial expression target (Tottenham et al., 2009), that is, the “go” stimulus (70 trials (73%)) and withhold their response to a facial expression non-target, the “nogo” stimulus (26 trials (27%)). Calm, happy, or fearful emotional facial expressions each served as the “go” stimulus during two runs for a total of six runs (happy go vs. fearful nogo, happy go vs. calm nogo, fearful go vs. calm nogo, fearful go vs. happy nogo, calm go vs. happy nogo, calm go vs. fearful nogo). Runs were pseudorandomized across participants. Cues appeared on the screen for 500 ms, with a 1500 ms interstimulus interval during which responses were recorded to give participants enough time to respond. Stimulus presentation and response collection was performed using E-Prime 1.0 or 2.0.

2.3 | Behavioral analysis

Data extraction was performed using Ruby version 2.1.0, and all statistical analyses were performed in R version 3.2.1 (R Core Team, 2015). Participants were included in the study if accuracy on

go-trials was > 50% and the percentage of false alarms during nogo-trials was <50% (below chance performance, $N = 35$ participants were excluded based on this criterion). Trials with RT's < 100ms were excluded from analysis as they were considered faster than participants could have visually processed cues (Luce, 1986). This censoring resulted in the inclusion of 377 individuals, for which a small number were included with partial data (valid data for only two ($N = 37$) or one ($N = 25$) emotion(s)) (Figure 1).

Mean and SD of the RT to correct go-trials was computed for each emotional expression. All three emotions (calm, fearful, and happy facial expressions) were presented as a go-stimulus twice during the six runs. RT's of the two runs of each emotion were collapsed. Ex-Gaussian parameters were computed (μ , σ , and τ) by fitting the ex-Gaussian distribution to the valid RT's on correct go-trials using the mexgauss function in the *retimes*-package in R (Heathcote, 1996). μ is defined as the mean and σ as the standard deviation from the normal (Gaussian) distribution of RT's, whereas τ is the mean and standard deviation of the exponential distribution. τ typically reflects positive skew in the raw RT distribution.

Response accuracy to each emotional expression was also computed, and is reported in Table S1. Accuracy per emotion was measured by calculating the number of hits to go-trials and false alarms to nogo-trials. The sensitivity index d' was computed by subtracting normalized false alarm rate from normalized accuracy at go-trials separately for all stimulus types (Macmillan & Creelman, 2004). As many participants performed at ceiling, accuracy to go-trials was transformed using a logit-transformation (Warton & Hui, 2011). Logit-transformed accuracy to go-trials was added to the designs in secondary analyses to explore the effects of accuracy on our RT findings.

2.4 | Investigating developmental effects: Continuous age-models

To understand the developmental differences of social emotional processing from 6 to 30 years of age, linear mixed-effects models were fit to the five measures (mean RT, SD RT, μ , σ and τ) of reaction times on the Emo Go-Nogo task with age (linear, cubic,

quadratic) growth models. An example of a full model, where d_i is within person dependence, that is, the repeated measures factor: Measurement = Intercept + d_i + $\beta 1(\text{emotion})$ + $\beta 2(\text{gender})$ + $\beta 3(\text{age})$ + $\beta 4(\text{age}^2)$ + $\beta 5(\text{age}^3)$ + $\beta 6(\text{emotion} * \text{age})$ + $\beta 7(\text{emotion} * \text{age}^2)$ + $\beta 8(\text{emotion} * \text{age}^3)$ + error.

The full procedure on determining choice for growth model can be found in the Supplemental Material.

2.5 | Investigating developmental effects: Sliding age bins

To assess the effects of social emotional cues on response latency during different developmental windows, participants were divided into age bins of 4 years using a sliding window with 1-year increments. While the continuous models show the general developmental pattern of RT, it is not sensitive to specific changes during smaller developmental windows, for example, young adulthood. We chose the sliding age bin approach to give a detailed estimate of the age-range in which possible effects of emotion on response latency occurred. Bins were not tested against each other due to the high number of overlapping participants in each bin. The number of participants within each age bin is plotted in Figure S1. Within each age bin, using the *lme4*-package in R, a linear mixed-effects (LME) model was fit with mean RT, *SD* RT, *mu*, *sigma*, and *tau* as dependent variables, emotion and gender as fixed factors, and within-subject dependence as a repeated measures random factor. The rationale for only including a random intercept at the subject-level was that some individuals were included with partial data in order to minimize the number of exclusions (Figure 1). In a secondary analysis, these models were repeated with logit-transformed accuracy as an additional factor in the design. P-values were corrected for multiple comparisons using the Benjamini–Hochberg procedure to control for the False Discovery Rate (FDR) (Benjamini & Hochberg, 1995). In the presence of a significant main effect of emotion, post hoc pairwise comparisons were performed using least-square means (*p*-values Tukey-adjusted). To explore the effects of gender on our results, analyses were repeated in males and females separately and reported in the supplemental text and Figure S2.

3 | RESULTS

3.1 | Developmental differences in emotion processing with continuous age-models

For mean, median and *SD* RT, *mu* and *tau*, a cubic age-model best fit the data (Figure 2a–e, full statistics in Tables S2–S7). The developmental pattern for mean and median RT and *mu* is characterized by a steep decline in RT during childhood, with an inflection point during mid-adolescence, after which RTs slightly increase again. Furthermore, there was an emotion*age³ interaction for mean ($F(6,670) = 3.3, p = .003$) and median RT ($F(6,668) = 3.2, p = .004$) and *mu* ($F(6,681) = 2.2, p = .042$). The developmental pattern of *sigma* was best characterized by a

quadratic age-model, showing a slightly later inflection point during young adulthood. Main effects of gender were only observed for *SD* RT ($F(1,356) = 6.2, p = .013$) and *tau* ($F(1,358) = 8.1, p = .005$) (Tables S4 and S7), indicating males were less variable than females. There were no interaction effects for *SD* RT, *sigma*, and *tau*.

3.2 | Developmental differences in emotion processing with sliding age bins

In every age bin, mean (Figure 3a, Table S8) and median RT (Table S9) showed slowing to fearful compared to happy and calm faces, which survived FDR-correction for multiple comparisons. *Mu* showed slower responses to fearful compared to happy and calm faces at 6–9, 13–16, and 15–18 years, all surviving FDR-correction for multiple comparisons (Figure 3b, Table S10).

SD RT showed greater variability to fearful facial expressions in the age-bins between 17 and 27 years of age, which survived corrections for multiple comparisons (Figure 3c, full results in Table S11). *Sigma* did not capture differences in RT variability between emotions (Figure 3d, Table S12). However, similar to *SD* RT, participants in the 19–22 and 20–23 age bins showed significantly increased *tau* to fearful faces. Additionally, *tau* was decreased toward happy compared to fearful facial expressions in the seven age bins between 17 and 26 years. (Figure 3e, full results in Table S13). The sliding age-bin analyses showed no effects of gender on any of the RT measures.

3.3 | Response accuracy

Mean accuracy to go-trials was high to each emotion (Table S1). Logit-transformed accuracy differed between the emotions ($F_{(2,670)} = 35.2, p < .001$), and increased with age ($F_{(1,352)} = 56.7, p < .001$), yet there was no interaction between emotion and age. Adding response accuracy to the continuous age models showed significant effects on mean ($F_{(1,827)} = 12.1, p < .001$), median ($F_{(1,816)} = 4.1, p = .044$), and *SD* RT ($F_{(1,1,005)} = 43.2, p < .001$), and on *sigma* ($F_{(1,1,012)} = 51.1, p < .001$) and *tau* ($F_{(1,1,036)} = 16.0, p < .001$), but not on *mu*. Nevertheless, adding accuracy did not meaningfully change the significance of the findings reported above, suggesting that the effects on reaction time and variability were not driven by developmental changes in accuracy. It must be noted that the logit-transformation improved the skew of the accuracy distribution, but not completely due to ceiling performance of many participants. Results including accuracy should therefore be interpreted with caution.

4 | DISCUSSION

Examining RT distributions with ex-Gaussian parameters in a dataset of 377 participants from age 6 through 30 years revealed developmental differences toward fearful faces. Adolescents had slower RTs to fearful faces as reflected by the ex-Gaussian

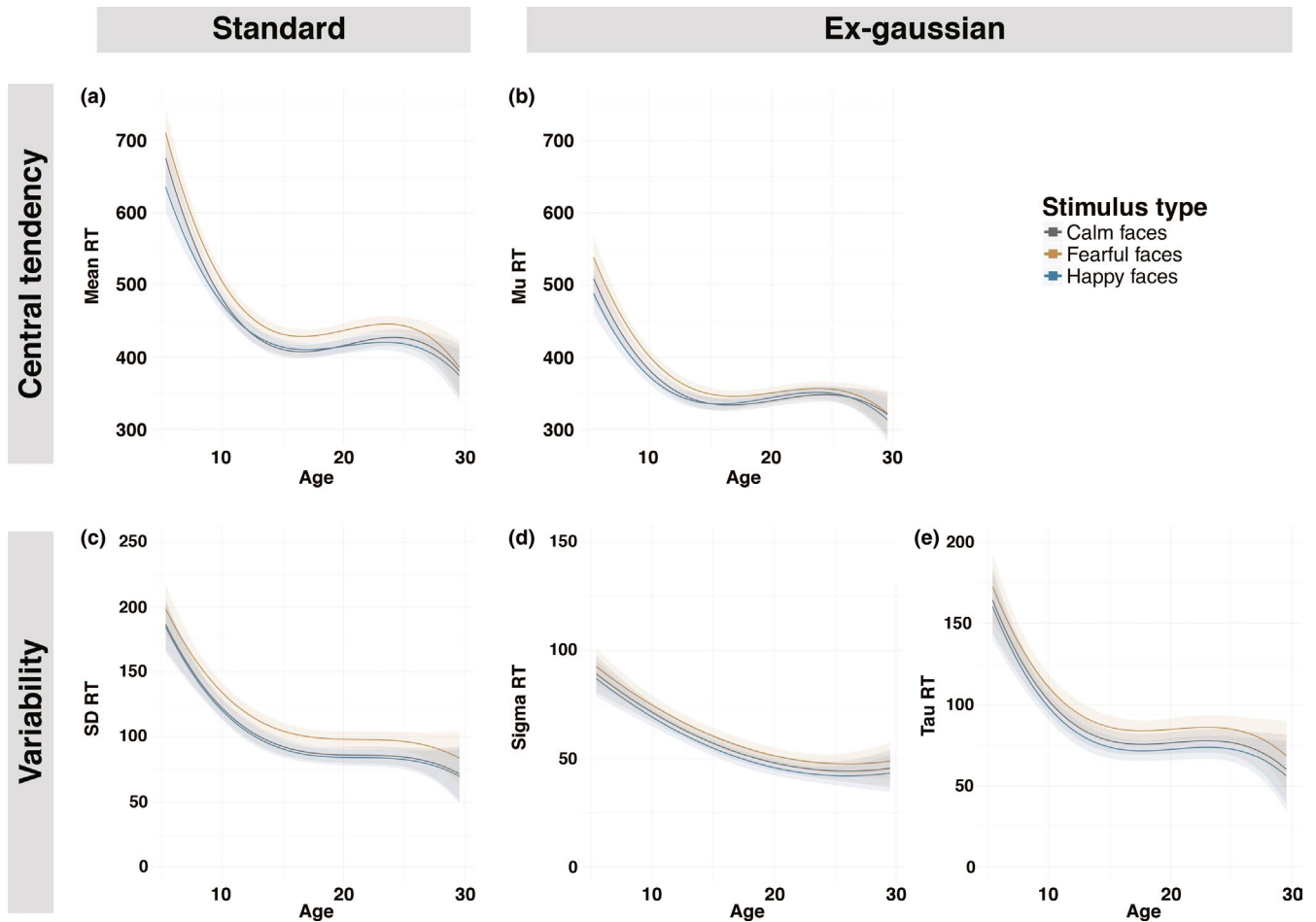


FIGURE 2 Results of the continuous age-models, with the top row showing measures of central tendency: (a) Mean RT (best age fit: cubic) and (b) the ex-Gaussian parameter μ (best age fit: cubic). The bottom row displays measures of intra-individual variability (c) SD (best age fit: cubic), (d) the ex-Gaussian parameter σ (best age fit: quadratic) and (e) the ex-Gaussian parameter τ (best age fit: cubic). Abbreviations: SD = standard deviation, RT = reaction time

statistic μ and young adults had more variability to fearful faces as reflected by increased SD RT and τ . The findings highlight the continued changes in social emotional processing that occur into early adulthood.

We found increased SD RT and τ to fearful facial expressions around young adulthood providing evidence for the continued refinement for processing emotional cues after adolescence (Casey et al., 2017; Cohen et al., 2016; Cohen-Gilbert et al., 2014; Silva, Shulman, Chein, & Steinberg, 2016). Notably, we did not observe differences between emotional cues on σ , but only on τ . The lack of an effect with σ suggests the ex-Gaussian parameters revealed distinct components of variability that were not captured by SD alone. It has tentatively been suggested that σ reflects variability in processing speed, whereas τ is related to attentional processing (Karalunas et al., 2014; Kofler et al., 2013; Schmiedek et al., 2007; Unsworth et al., 2010). Our finding of increased τ to fearful cues compared to happy or calm cues may suggest enhanced attentional capture to fearful cues in young adults. Increased interference during identification and processing of relevant cues has been associated with slower responses (Provost, Jamadar, Heathcote, Brown, &

Karayanidis, 2018; Weissman, Roberts, Visscher, & Woldorff, 2006). Attentional control theory suggests that responses to emotional cues are driven by automatic, bottom-up, salience-driven processing on one hand and top-down, goal-directed attentional processing on the other (Eysenck & Derakshan, 2011; Eysenck, Derakshan, Santos, & Calvo, 2007). The infrequent long RTs toward fearful facial expressions could then be hypothesized to reflect the more top-down, deliberative nature in which young adults fine-tune their response to emotionally valenced cues (Cohen-Gilbert et al., 2014; Silvers, Shu, Hubbard, Weber, & Ochsner, 2015). It has also been suggested that increased intra-individual variability may reflect exploration of diverse strategies, which has been related to increased success on completing complex tasks (MacDonald et al., 2009; Tamnes et al., 2012). As such, increased intra-individual variability, here captured by τ , may reflect more explicit cognitive strategies, and increased cognitive resources, that young adults use during social emotion processing.

In line with previous developmental work, every age bin showed mean and median RT were slowest toward fearful cues (Cohen-Gilbert & Thomas, 2013; Grose-fifer et al., 2013; Tottenham et al., 2011), suggestive of a general sensitivity to fearful facial

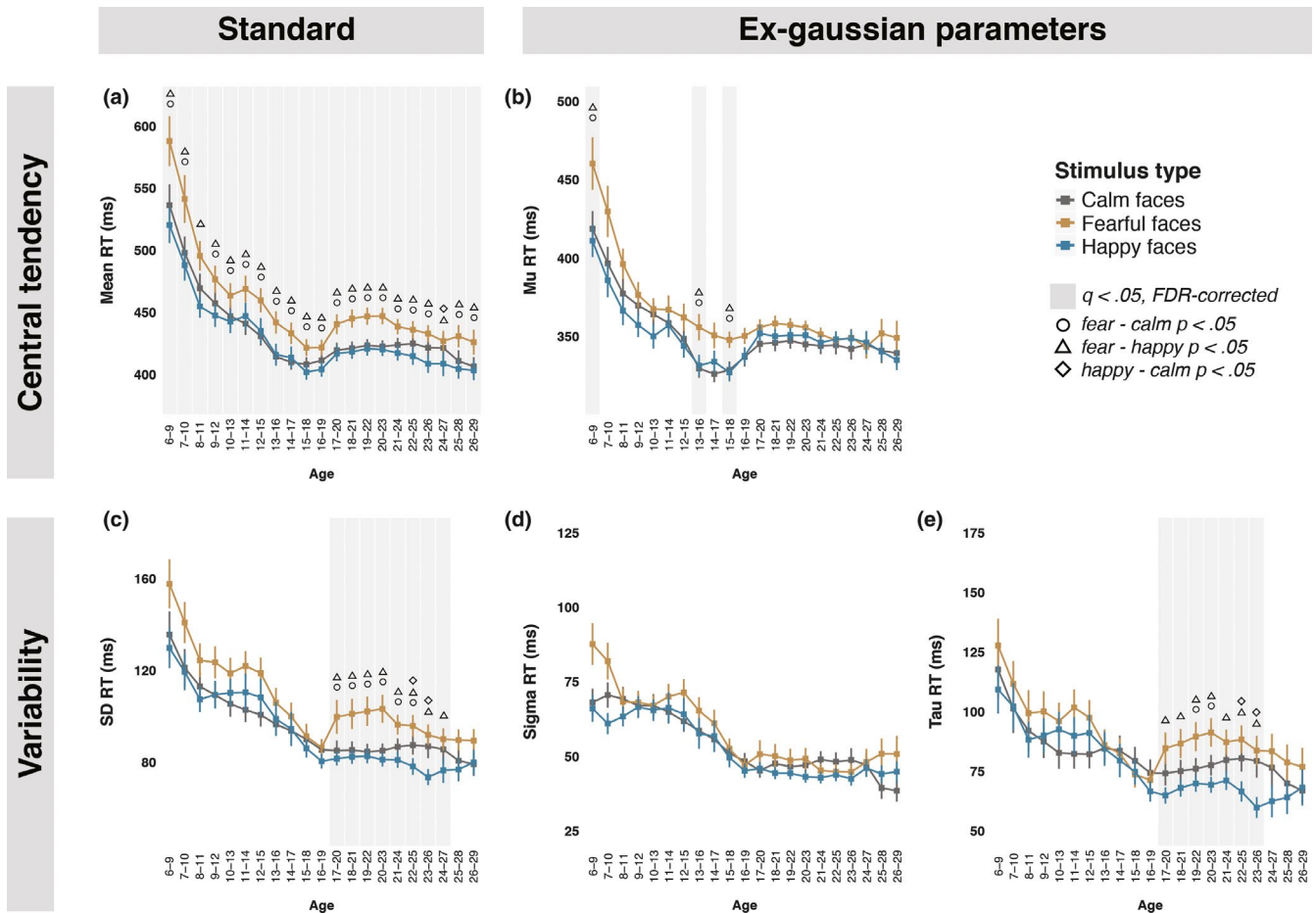


FIGURE 3 Results of the age-bin analyses, with the top row showing measures of central tendency (a) Mean RT and (b) the ex-Gaussian parameter μ . The bottom row displays measures of intra-individual variability (c) SD, (d) the ex-Gaussian parameter σ , and (e) the ex-Gaussian parameter τ . Asterisks denote significant main effects of emotion (Tables S9–S13), gray bars indicate that the effect survived FDR-correction for multiple comparisons. Error bars denote ± 1 SE. Abbreviations: FDR = False Discovery Rate, SD = standard deviation, RT = reaction time

expressions across development. In contrast to the measures of central tendency, the ex-Gaussian parameter μ showed a specific differentiation according to the emotional valence of cues in very young children and adolescents only. The ex-Gaussian parameter μ suggests that adolescents were slower to respond to fearful compared to happy or calm expressions, possibly reflecting heightened bottom-up, salience-driven interference by negatively valenced cues during this developmental phase (Grose-fifer et al., 2013).

The sliding age bin method showed sensitivity to the influence of negative emotion on RT and RT variability in specific age-ranges, however, development is a more continuous process that is of course not restrained by the age-bins used in the current study. Adding to the sliding age bin analyses, the growth models revealed that the measures of central tendency (mean and median RT, and μ) showed an interaction between emotion and age, suggesting developmental differences in how RT is modulated by emotional valence. Conversely, we found no differences the general shape of the developmental trajectories of variability (SD RT, σ and τ), which showed similar curves for all emotions,

consistent with the inverted U-shaped trajectory that has been observed across the lifespan (Fagot et al., 2018; Li et al., 2004; Williams et al., 2005). The findings from the continuous models provide normative developmental data for the influence of emotion on different aspects of RT and RT variability across development. RT variability has been proposed to be a powerful proxy for general brain development (Adleman et al., 2016; Carp, Fitzgerald, Taylor, & Weissman, 2012; Tamnes et al., 2012; Yarkoni, Barch, Gray, Conturo, & Braver, 2009), and decreased RT variability has been associated with increased cognitive flexibility (Garrett et al., 2011; McIntosh et al., 2008) and attentional control (Johnson et al., 2015). The ground work established from our findings can provide the foundation for future longitudinal studies that examine how the trajectories for social emotional processing may differ in neurodevelopmental disorders.

The findings are consistent with recent neurobiological models of development. The "imbalance" model suggests the development of emotional responsivity follows a pattern of continuous, but hierarchical change into adulthood. Within this framework it is hypothesized that connectivity within and between cortical and sub-cortical

systems matures in such a way that each developmental phase is in part dependent on the previous phase (Casey et al., 2017). In adolescence, the establishment of reciprocal subcortico-cortical connections is characterized by more automatic heightened sensitivity to emotional cues (Silvers et al., 2017; Somerville et al., 2011), which transitions into more controlled top-down regulation of emotion into young adulthood (Braunstein, Gross, & Ochsner, 2017; Silvers et al., 2016) through cortico-cortical connections. The increased variability, captured by *SD* RT and *tau*, to fearful faces in the current study could indeed reflect the transition into a subsequent phase in development where emotion regulation is more effectively modulated within cortical circuitry.

Taken together, the current findings add to a large body of literature on the influence of emotional information on adolescent self-regulation (Cohen-Gilbert & Thomas, 2013; Dreyfuss et al., 2014; Grose-fifer et al., 2013; Hare et al., 2008; Somerville et al., 2011; Tottenham et al., 2011), by suggesting that young adults continue to show reactivity to negatively valenced emotional information (Cohen et al., 2016). This heightened reactivity may have implications for understanding the emergence of mental health problems, with anxiety disorders showing their first onset in late childhood, and depression emerging around early adulthood (Lee et al., 2014; Powers & Casey, 2015). Future work should explore the relationship between variable processing of negative facial expressions and susceptibility for mental health problems in young adults.

Our findings should be interpreted in light of limitations of the study. Although the sliding age-bin analyses examined changes in emotion processing in small time windows, the definition of these windows does not fully appreciate the continuous nature of development. As such, we used continuous age-models that showed the developmental pattern of mean reaction time and were differentially modulated by emotion development. Furthermore, the ex-Gaussian model does not take into account response accuracy, but adding response accuracy to the design did not change the findings. Lastly, the 2000ms total trial-duration is longer than other go/nogo tasks which may have influenced performance on this task, and other types of tasks may better capture RT to emotional cues as a go/nogo paradigm does not collect RTs for all trials. However, results show that the timing and design made the task accessible and engaging to young children, as reflected by the low number of children that had to be excluded based on poor performance.

In conclusion, the findings suggest protracted development of social emotional processing, showing that response speed and variability were differentially modulated by emotional information in adolescents and young adults. These findings fit with recent suggestions of circuit-based hierarchical development of emotional processing, demonstrating that in addition to adolescence, young adulthood is a developmental phase that is associated with distinct processing for emotional cues relative to older adults. Future work examining how difficulties with emotion reactivity, commonly associated with anxiety and mood disorders, emerge at different time points across development including the teen years and into the mid-20's will be important avenues of research.

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CONFLICTS OF INTEREST

All authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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