

EXHIBIT 63

Association of Habitual Checking Behaviors on Social Media With Longitudinal Functional Brain Development

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 Supplemental content

IMPORTANCE Social media platforms provide adolescents with unprecedented opportunities for social interactions during a critical developmental period when the brain is especially sensitive to social feedback.

OBJECTIVE To explore how adolescents' frequency of checking behaviors on social media platforms is associated with longitudinal changes in functional brain development across adolescence.

DESIGN, SETTING, AND PARTICIPANTS A 3-year longitudinal cohort study of functional magnetic resonance imaging (fMRI) among sixth- and seventh-grade students recruited from 3 public middle schools in rural North Carolina.

EXPOSURES At wave 1, participants reported the frequency at which they checked Facebook, Instagram, and Snapchat.

MAIN OUTCOME OR MEASURE Neural responses to the Social Incentive Delay task when anticipating receiving social feedback, measured annually using fMRI for 3 years. Participants saw a cue that indicated whether the social feedback (adolescent faces with emotional expressions) would be a reward, punishment, or neutral; after a delay, a target appeared and students responded by pressing a button as quickly as possible; a display of social feedback depended on trial type and reaction time.

RESULTS Of 178 participants recruited at age 12 years, 169 participants (mean [SD] age, 12.89 [0.58] years; range, 11.93-14.52 years; 91 [53.8%] female; 38 [22.5%] Black, 60 [35.5%] Latinx, 50 [29.6%] White, 15 [8.9%] multiracial) met the inclusion criteria. Participants with habitual social media checking behaviors showed lower neural sensitivity to social anticipation at age 12 years compared with those with nonhabitual checking behaviors in the left amygdala, posterior insula (PI), and ventral striatum (VS; β , -0.22; 95% CI, -0.33 to -0.11), right amygdala (β , -0.19; 95% CI, -0.30 to -0.08), right anterior insula (AI; β , -0.23; 95% CI, -0.37 to -0.09), and left dorsolateral prefrontal cortex (DLPFC; β , -0.29; 95% CI, -0.44 to -0.14). Among those with habitual checking behaviors, there were longitudinal increases in the left amygdala/PI/VS (β , 0.11; 95% CI, 0.04 to 0.18), right amygdala (β , 0.09; 95% CI, 0.02 to 0.16), right AI (β , 0.15; 95% CI, 0.02 to 0.20), and left DLPFC (β , 0.19; 95% CI, 0.05 to 0.25) during social anticipation, whereas among those with nonhabitual checking behaviors, longitudinal decreases were seen in the left amygdala/PI/VS (β , -0.12; 95% CI, -0.19 to -0.06), right amygdala (β , -0.10; 95% CI, -0.17 to -0.03), right AI (β , -0.13; 95% CI, -0.22 to -0.04), and left DLPFC (β , -0.10; 95% CI, -0.22 to -0.03).

CONCLUSIONS AND RELEVANCE The results of this cohort study suggest that social media checking behaviors in early adolescence may be associated with changes in the brain's sensitivity to social rewards and punishments. Further research examining long-term associations between social media use, adolescent neural development, and psychological adjustment is needed to understand the effects of a ubiquitous influence on development for today's adolescents.

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In the span of a generation, social media has dramatically changed the landscape of adolescent development, providing unprecedented opportunities for social interactions around the clock.¹ Social media provides a constant and unpredictable stream of social inputs to adolescents during a critical developmental period when the brain becomes especially sensitive to social rewards and punishments.² Motivated by the anticipation of this social feedback, adolescents' constant, habitual checking of social media may alter neurodevelopment, significantly changing the ways in which the adolescent brain responds to its environment.

Social media allows immediate access to social information at any time it is desired^{1,3,4} and is designed to hold users' engagement by maximizing social rewards. "Likes," notifications, and messages arrive unpredictably on a maximally powerful variable reinforcement schedule, conditioning individuals to check social media habitually in anticipation of this social feedback.⁵ With 78% of 13- to 17-year-olds reporting checking their devices at least hourly⁶ and 46% checking "almost constantly,"⁷ adolescents may be uniquely vulnerable to habitual checking behaviors.

The brain undergoes significant structural and functional reorganization during adolescence.⁸ Neural regions involved in motivational relevance (eg, the ventral striatum; VS) and affective salience (eg, the amygdala and insula) become hyperactive, orienting teens to rewarding stimuli in their environment, particularly from peers.⁹⁻¹⁴ Adolescents' habitual checking of social media may be exacerbating an already enhanced neural response to the anticipation of salient social feedback. Additionally, the motivational salience of social contexts may undermine adolescents' ability to engage in cognitive control and, subsequently, to regulate their behaviors.¹⁵ Consequently, repeated exposure to digital social rewards (eg, notifications or likes) may increase neural reactivity to reward-related cues, reducing adolescents' ability to resist urges to check social media.^{16,17}

The current study aimed to examine whether social media use is associated with longitudinal changes in functional brain development across adolescence, a developmental period characterized by peak social media use¹⁸ and heightened neural sensitivity to social feedback from peers.⁸ We hypothesized that checking social media habitually would make adolescents increasingly hypersensitive to social feedback anticipation and thus would be associated with longitudinal increases in neural activation, particularly within regions comprising the motivational (eg, VS), affective salience (eg, insula and amygdala), and cognitive control (eg, dorsolateral prefrontal cortex; DLPFC) networks. Conversely, we hypothesized that nonhabitual checking would be associated with longitudinal decreases in neural activation in the same brain regions. Given the limited research exploring longitudinal neural activation in relation to social media behaviors, we conducted exploratory whole-brain analyses to determine which brain regions showed the greatest differences in neural activation longitudinally. To our knowledge, results from this study would provide the first insight into how habitual social media behaviors may be altering adolescent brain development.

Key Points

Question Is adolescents' frequency of checking behaviors on 3 social media platforms (Facebook, Instagram, Snapchat) associated with longitudinal changes in functional brain development across adolescence.

Findings In this cohort study of 169 sixth- and seventh-grade students, participants who engaged in habitual checking behaviors showed a distinct neurodevelopmental trajectory within regions of the brain comprising the affective salience, motivational, and cognitive control networks in response to anticipating social rewards and punishments compared with those who engaged in nonhabitual checking behaviors.

Meaning These results suggest that habitual checking of social media in early adolescence may be longitudinally associated with changes in neural sensitivity to anticipation of social rewards and punishments, which could have implications for psychological adjustment.

Methods

Participants

Participants were recruited from a larger, school-based study of 873 sixth- and seventh-grade students from 3 public rural middle schools in North Carolina to participate in a longitudinal functional magnetic resonance imaging (fMRI) study. We recruited 2 cohorts of participants at 12 to 13 years of age across 2 years of the study, leading to a sample size of 178 adolescents (148 students for cohort 1 and 30 for cohort 2). Of the recruited participants for cohort 1, 5 met exclusion criteria after consenting to the study and thus were excluded and not invited back for later waves (see the eMethods in the [Supplement](#) for exclusion criteria). Across all waves, 25 participants completed 1 time point, 36 completed 2 time points, and 112 completed 3 time points. All participants provided written informed consent or assent, and the University's Institutional Review Board approved all aspects of the study. Race and ethnicity were self-reported by participants. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. For more information on study procedures, see the eMethods in the [Supplement](#).

Self-reported Social Media Use

Participants reported frequency of checking at wave 1 only. For 3 popular social media platforms (Facebook, Instagram, and Snapchat), participants were asked how many times per day they checked each platform, with answers grouped into 8 numerical score categories (1, <1 time per day; 2, 1 time per day; 3, 2-3 times per day; 4, 4-5 times per day; 5, 6-10 times per day; 6, 11-15 times per day; 7, 16-20 times per day; 8, >20 times per day). We recoded participants' scores to create an ordinal scale that captured social media checking frequency across a meaningful distribution that could be assessed quantitatively. A score of 1 was recoded to 0 and a score of 2 was recoded to 1. Scores between 3 and 7 were recoded to the average of the range of

number of times checked; for example, if participants selected 6 for their Facebook use (ie, checked Facebook between 11 and 15 times per day), then their score was recoded to the average of 11 and 15 times, which in this case was 13 times checked. Reported scores of 8 (ie, checked >20 times per day) were recoded to 20 times checked. For each participant, the recoded checking behaviors on the 3 social media platforms were summed to create a total social media checking score that ranged from 0 to 54 (mean [SD] checking behaviors per day, 11.85 [15.39]).

Social Incentive Delay Task

At each wave, participants attended a brain imaging session during which they completed the Social Incentive Delay task while undergoing fMRI to measure neural responses when anticipating receiving social rewards and avoiding social punishments.^{19,20} On each trial, participants saw a cue (for 500 milliseconds) indicating whether the potential social feedback would be a reward, punishment, or neutral. After a variable delay (mean delay, 2000 milliseconds; range, 480-3900 milliseconds), a target appeared (for 300 milliseconds), at which point participants were instructed to respond by pressing a button as quickly as possible. The display of social feedback (for 1450 milliseconds) depended on the trial type and participants' reaction time. In the social reward condition, happy faces were the outcome of a fast response (hit), and blurred faces were the outcome of a slow response (miss). In the social punishment condition, a hit earned a blurred face, and a miss earned an angry face. In the control condition, a blurred face was always the outcome for both hits and misses. Trials were presented in an event-related design, with reward, punishment, and neutral trials randomly ordered. Participants completed 2 rounds of the task, totaling 116 trials (48 reward, 48 punishment, and 20 neutral trials).

Task difficulty was standardized to a hit rate of approximately 50% for all participants by adjusting target duration to individual reaction times. Age-matched adolescent faces with emotional expressions of 24 ethnically diverse people (12 female) were used as reward and punishment stimuli. Photographs were taken from the National Institute of Mental Health Child Emotional Faces Picture Set. Participants were trained on the meaning of each cue and completed 12 practice trials prior to entering the scanner.

Statistical Analysis

fMRI Data Acquisition

Imaging data were collected using a 3-T Magnetom Prisma MRI scanner (Siemens Healthineers). For specific fMRI image acquisition parameters and preprocessing methods, see the eMethods in the Supplement. Individual level, fixed-effects analyses were estimated using the general linear model convolved with a canonical hemodynamic response function in Statistical Parametric Mapping software package SPM12 (Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology). The task was modeled as event related with 8 conditions, including 3 anticipation conditions (reward, punishment, and neutral), 2 outcome conditions for both reward (hit or miss) and punishment (hit or miss), and 1 out-

come condition for neutral. Anticipation conditions were modeled as the onset of the cue and a duration of zero, and outcome conditions were modeled at the onset of the outcome with a duration of zero. Six motion parameters were modeled as nuisance regressors. Using the general linear model, linear contrast images comparing each of the conditions of interest were calculated for each individual. The primary contrasts of interest for this study were reward anticipation vs neutral anticipation and punishment anticipation vs neutral anticipation, given our supposition that checking behaviors on social media platforms is motivated by the anticipation of social feedback.

Longitudinal Whole-Brain Analyses

We conducted longitudinal whole-brain analyses using the 3dLMEr program (AFNI).²¹ This program allows for voxel-level whole-brain analysis of linear mixed effects (maximum likelihood, multilevel model). Missing data across waves were accounted for by using full information maximum likelihood, which provides an estimate of the value of a population parameter most likely to result in the observed data even in the presence of missing data.²² We modeled a 3-way interaction with age (minimum centered), condition (reward and punishment anticipation), and social media checking to assess whether age-related changes in neural activation during social anticipation differed as a function of the type of social anticipation (ie, reward vs punishment) and amount of social media checking behaviors. To correct for multiple comparisons, we conducted a Monte Carlo simulation using the 3dFWHMx and 3dClustSim programs (AFNI)²³ and the group-level brain mask. Smoothness was estimated with the -acf option (-acf a, b, and c parameters 0.55, 4.61, 12.32), which used an average of individual-level autocorrelation function parameters (obtained using each participant's residuals from the first-level model). This simulation indicated that a $P < .05$ family-wise error corrected would be achieved with a voxelwise threshold of $P < .001$ and a minimum cluster size of 80 voxels. A 2-sided $P < .01$ indicated statistical significance.

To explore any significant whole-brain interactions and plot the trajectories, we extracted parameter estimates from significant clusters. Parameter estimates were fitted into a conditional linear trajectory model whereby these post hoc analyses allowed us to unpack the significant 3-way interaction between age, condition, and social media checking behavior. For plotting purposes, we categorized the total social media checking scores as high (>15; habitual), moderate (1-15), and low (0; nonhabitual). This allowed us to test whether trajectories of neural response differed as a function of anticipation type and amount of social media checking.

Results

After exclusions, the final sample size was 169 (mean [SD] age, 12.89 [0.58] years; range, 11.93-14.52 years; 91 [53.8%] female; 38 [22.5%] Black, 60 [35.5%] Latinx, 50 [29.6%] White, 15 [8.9%] multiracial [2 or more racial categories identified other Hispanic or Latinx], and 6 [3.6%] categorized as other

Table. Age-Related Neural Changes as a Function of Social Media Checking During Anticipation of Social Feedback

Anatomical region	MNI coordinates ^a			t statistic	Cluster size, voxels ^b
	x	y	z		
Posterior insula	34	6	-4	46.1	2038
Left amygdala	-26	-2	-12	46.1	2038
Ventral striatum	-24	14	-4	46.1	2038
Orbitofrontal cortex	-20	-8	-18	38.3	1027
Right amygdala	22	4	-18	38.3	1027
Cerebellum	0	80	-32	30.3	736
Thalamus	12	26	0	35.3	640
Frontal operculum	-56	-14	-8	31.8	606
Anterior insula	36	22	-4	31.8	606
Middle cingulate cortex	-18	38	38	41.4	534
Dorsolateral prefrontal cortex	42	-42	28	44.1	501
Globus pallidus	34	2	66	27.1	456
Inferior temporal gyrus	-58	38	-22	45.9	374
Postcentral gyrus	54	16	28	31.1	369
Hippocampus	-32	8	-32	26	235
Somatosensory area	-60	8	38	26.5	179
Superior temporal gyrus	60	32	12	26.3	177
Supramarginal gyrus	44	36	28	25.3	153
Cerebellar vermis	-4	50	-6	26.8	143
Intraparietal sulcus	-22	88	16	19.1	116
Supplementary motor area	-8	-4	44	20.7	114
Inferior parietal lobule	-52	42	56	27.5	106
Cuneus	12	86	34	23.4	102
Anterior inferior parietal lobule	-50	34	38	23.9	102
Intraparietal sulcus	-38	58	50	20.5	91

Abbreviation: MNI, Montreal Neurological Institute.

^a Values are the MNI coordinates to regions of the brain that changed significantly over age.

^b Clusters that survived cluster-extent threshold correction when modeling longitudinal whole-brain changes in sensitivity to social anticipation as a function of social media checking behaviors, assessed using the 3dLMEr program (AFNI). Multiple brain regions may lie within the same brain cluster.

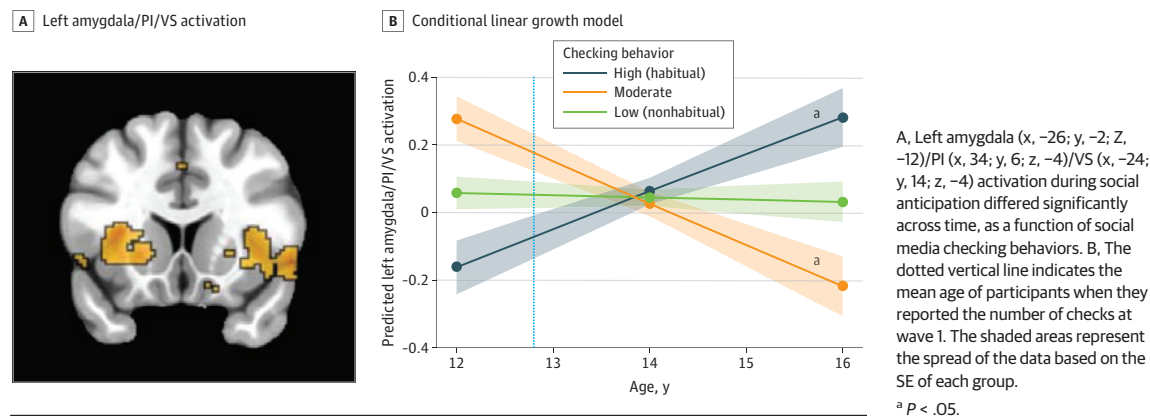
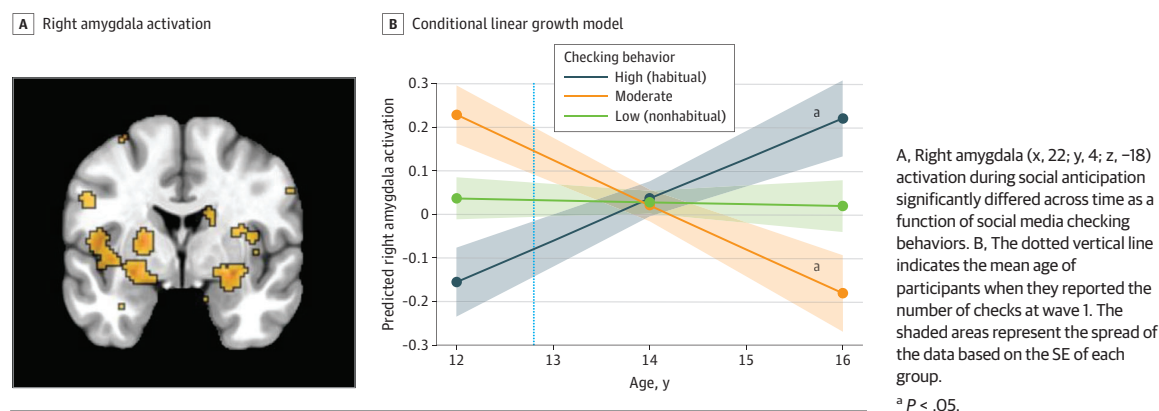
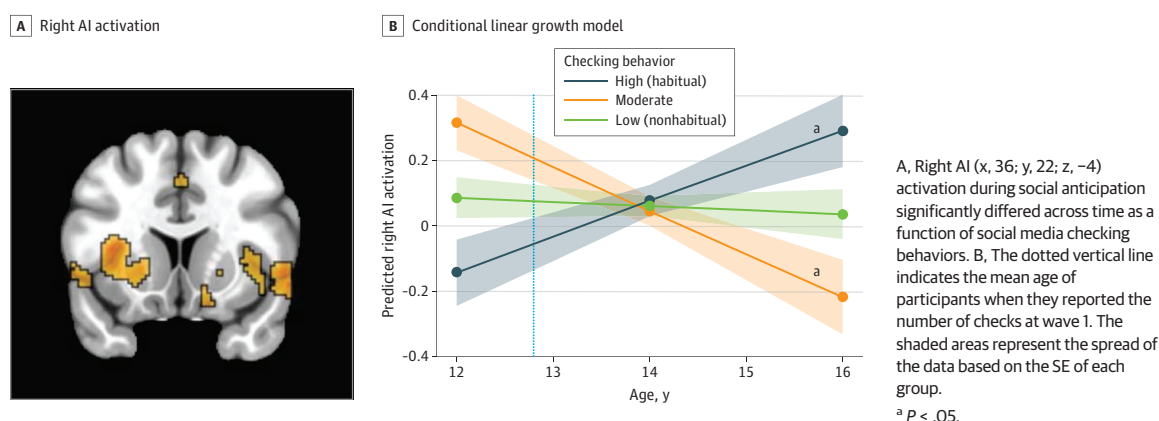
[American Indian or Alaska Native, Asian, and Native Hawaiian or other Pacific Islander]) collected across 3 waves; 136 participants completed wave 1 (mean [SD] age, 12.80 [0.52] years; range, 11.9-14.5 years; 71 [52.2%] female), 131 participants completed wave 2 (mean [SD] age, 13.7 [0.59] years; range, 12.4-15.4 years; 68 [51.9%] female), and 124 participants completed wave 3 (mean [SD] age, 14.70 [0.60] years; range, 13.4-16.3 years; 61 [49.2%] female). The mean (SD) time between waves 1 and 2 was 49.8 (3.9) weeks, and that between waves 2 and 3 was 52.9 (6.9) weeks. Retention was 81.1% from waves 1 to 2 and 85.3% from waves 2 to 3. Adolescents reported checking behaviors on 3 social media platforms at wave 1 only. For descriptive statistics regarding checking behaviors on all 3 platforms, see the eFigure in the Supplement. Checking behaviors within the 3 apps were recoded and summed for a total social media checking score, which ranged from 0 to 54 mean (SD) score, 11.85 (15.39).

Using 3dLMEr to model longitudinal whole-brain changes in sensitivity to social anticipation, there was not a 3-way interaction between type of social anticipation, age, and social media checking behavior, so we collapsed social reward and social punishment. We found significant 2-way interactions between age and social media checking behaviors in several regions, including the posterior insula (PI; x, 34; y, 6; z, -4), the left amygdala (x, -26; y, -2; z, -12), the VS (x, -24; y, 14; z, -4), the right amygdala (x, 22; y, 4; z, -18), anterior insula (AI; x,

36; y, 22; z, -4), and the DLPFC (x, 42; y, -42; z, 28) (Table). Of particular interest were the left amygdala extending into the PI and VS (Figure 1A), the right amygdala (Figure 2A), right AI (Figure 3A), and left DLPFC (Figure 4A). Significant 2-way interactions between age and social media checking behaviors were found in similar brain regions when receiving social feedback (eTable in the Supplement).

We extracted parameter estimates from each participant at each wave from the significant clusters in order to unpack the 2-way interaction. We ran post hoc conditional linear growth models to compare the trajectories of adolescents who engaged in low (nonhabitual; n = 79), moderate (n = 34), or high (habitual; n = 56) social media checking behaviors. Participants with high (habitual) checking behaviors showed a lower neural sensitivity to social anticipation at age 12 years (ie, the intercept) compared with those with low (nonhabitual) checking behaviors in the left amygdala/PI/VS (β , -0.22; 95% CI, -0.33 to -0.11 [Figure 1B]), right amygdala (β , -0.19; 95% CI, -0.30 to -0.08 [Figure 2B]), right AI (β , -0.23; 95% CI, -0.37 to -0.09 [Figure 3B]), and left DLPFC (β , -0.29; 95% CI, -0.44 to -0.14 [Figure 4B]). Here, β values refer to the main result of checking behavior at age 12 years where negative values indicate lower neural activation with higher checking behavior.

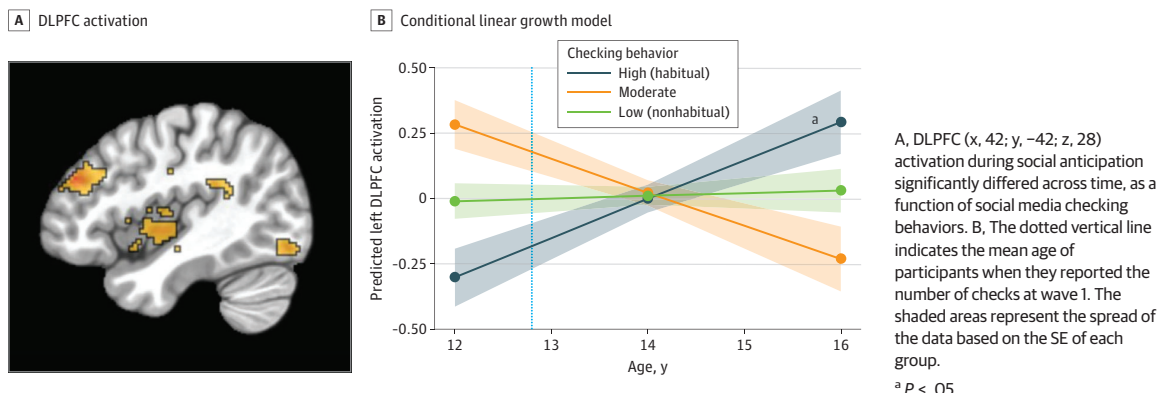
Developmentally, participants with high checking behaviors at age 12 years showed longitudinal increases (ie, the lin-

Figure 1. Functional Activation in the Left Amygdala, Posterior Insula (PI), and Ventral Striatum (VS) During the Anticipation of Social Feedback**Figure 2. Functional Activation in the Right Amygdala During the Anticipation of Social Feedback****Figure 3. Functional Activation in the Right Anterior Insula (AI) During the Anticipation of Social Feedback**

ear slope) in neural sensitivity in the left amygdala/PI/VS (β , 0.11; 95% CI, 0.04 to 0.18 [Figure 1B]), right amygdala (β , 0.09; 95% CI, 0.02 to 0.16 [Figure 2B]), right AI (β , 0.15; 95% CI, 0.02 to 0.20 [Figure 3B]), and left DLPFC (β , 0.19; 95% CI, 0.05 to

0.25 [Figure 4B]). Participants with low checking behaviors showed significant longitudinal decreases in neural sensitivity in the left amygdala/PI/VS (β , -0.12; 95% CI, -0.19 to -0.06 [Figure 1B]), right amygdala (β , -0.10; 95% CI, -0.17 to -0.03

Figure 4. Functional Activation in the Left Dorsolateral Prefrontal Cortex (DLPFC) During the Anticipation of Social Feedback



[Figure 2B]), right AI (β , -0.13 ; 95% CI, -0.22 to -0.04 [Figure 3B]), and small decreases in the left DLPFC (β , -0.10 , 95% CI, -0.22 to -0.03 [Figure 4B]). Here, β represents the age-related change in neural activation for each group. Results suggest that trajectories of neural sensitivity to anticipation of social feedback for habitual and nonhabitual checkers are inversely related.

Discussion

This cohort study examined whether early adolescents' frequency of checking behaviors on 3 popular social media platforms (Facebook, Instagram, and Snapchat) was associated with trajectories of functional brain development across adolescence. Adolescents who engaged in high (habitual) checking behaviors showed distinct neural trajectories when anticipating social feedback compared with those who engaged in moderate or low (nonhabitual) checking behaviors, suggesting that habitual social media checking early in adolescence is associated with divergent brain development over time.

We found that 12-year-old adolescents showed different neural patterns based on their social media checking behavior. While participants with habitual checking behaviors demonstrated hypoactivation of the amygdala, PI, VS, and DLPFC in response to anticipation of social feedback, those with nonhabitual behaviors demonstrated hyperactivation in these same brain regions. Interestingly, these patterns diverged across development, with those with habitual behaviors showing longitudinal increases in activation in these regions and those with nonhabitual behaviors showing longitudinal decreases in activation.

Longitudinal decreases in neural activation among participants with nonhabitual checking behaviors may indicate a developmentally normative decreasing sensitivity to social anticipation. Indeed, prior research^{12,24-27} has found that in response to social anticipation, early adolescents show an initial hypersensitivity, followed by a decrease in activation of the PI and VS, brain regions associated with salience and motivation, respectively. Additionally, activation of the DLPFC dur-

ing inhibitory control normatively decreases across adolescence.²⁸ Decreasing DLPFC activation observed among nonhabitual checkers may indicate that these adolescents are better able to control impulsive or habitual behaviors, such as checking social media, and thus recruit prefrontal cortical regions less over time. In contrast, those with habitual checking behaviors showed longitudinal increases in neural activation in the amygdala, VS, PI, and DLPFC. Research has shown that with constant reinforcement, dopaminergic neurons within salience-related brain regions (ie, the VS, PI, and amygdala) become increasingly responsive to social feedback,²⁹ and the enhanced value of rewards in the salience and motivation networks may override inhibitory control exerted by the PFC and cause a positive-feedback loop.³⁰ The observed increase in DLPFC activation may indicate that more effort is required for cognitive control when anticipating social feedback.

Our findings suggest that checking behaviors on social media in early adolescence may tune the brain's sensitivity to potential social rewards and punishments. Whereas individuals with habitual checking behaviors showed initial hypoactivation but increasing sensitivity to potential social cues over time, those with nonhabitual checking behaviors showed initial hyperactivation and decreasing sensitivity over time. Two primary theories contend over whether hypo- or hyperresponsivity to rewards is more associated with behavior.³¹ The hyperresponsive theory posits that adolescent reward-associated behaviors are associated with greater activation of the ventral-striatal dopamine circuit.^{11,24,32} Consequently, adolescents would experience an increased dopaminergic release in response to social feedback and rewards, which further encourages high-reward behaviors. Indeed, compared with children and adults, adolescents show higher activation in the reward system when receiving rewards.^{10-12,24,26} In contrast, the hyporesponsive theory posits that adolescent reward-seeking behaviors may be associated with a deficit in the activity of brain regions associated with motivation.^{30,33} This theory argues that repeated exposure to a social reward down-regulates dopamine receptors and production, which results in decreased sensitivity of reward circuits. Studies^{34,35} sug-

gest that, as adolescents experience fewer or less intense positive feelings from previously rewarding stimuli, they are driven to pursue new appetitive reinforcements through increases in reward-seeking behaviors, which increases activity in dopamine-related circuitry. Indeed, relative to adults, adolescents show less engagement of the VS in anticipation of rewards.^{30,36} While for some individuals with habitual checking behaviors, an initial hyposensitivity to potential social rewards and punishments followed by hypersensitivity may contribute to checking behaviors on social media becoming compulsive and problematic, for others, this change in sensitivity may reflect an adaptive behavior that allows them to better navigate their increasingly digital environment.

Limitations

This study has limitations. Notably, because differences in neural trajectories already existed between participants with habitual and nonhabitual checking behaviors at the start of the study, it is difficult to determine whether social media use prior to data collection caused these distinct neural trajectories or preexisting differences in neural activation placed some youth at risk for more habitual checking behaviors. Future studies

should explore the neurodevelopmental trajectories of social feedback responsiveness from an earlier age to uncover causal pathways behind this association. Moreover, examination of social media checking behaviors across time is needed to further elucidate associations with development. Finally, future work should examine functional connectivity to explore how affective salience, motivational, and cognitive control networks coactivate and function at a network level.

Conclusions

Adolescent social media use has proliferated extensively in the past decade. This longitudinal cohort study suggests that social media behaviors in early adolescence may be associated with changes in adolescents' neural development, specifically neural sensitivity to potential social feedback. Further research examining long-term prospective associations between social media use, adolescent neural development, and psychological adjustment is needed to understand the effects of a ubiquitous influence on development for today's adolescents.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Maza, Fox, Kwon, Lindquist, Prinstein, Telzer.

Critical revision of the manuscript for important intellectual content: Maza, Fox, Flannery, Lindquist, Prinstein, Telzer.

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