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Maternal dopamine encodes affective signals of human infants

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Abstract

Mothers are highly responsive to their offspring. In non-human mammals, mothers secrete dopamine in the nucleus accumbens (NAcc) in response to their pups. Yet, it is still unknown which aspect of the offspring behavior elicits dopaminergic responses in mothers. Here, we tested whether infants' affective signals elicit dopaminergic responses in the NAcc of human mothers. First, we conducted a behavioral analysis on videos of infants' free play and quantified the affective signals infants spontaneously communicated. Then, we presented the same videos to mothers during a magnetic resonance-positron emission tomography scan. We traced the binding of [^{11}C]raclopride to free $D_{2/3}$-type receptors to assess maternal dopaminergic responses during the infant videos. When mothers observed videos with many infant signals during the scan, they had less [^{11}C]raclopride binding in the right NAcc. Less [^{11}C]raclopride binding indicates that less $D_{2/3}$ receptors were free, possibly due to increased endogenous dopamine responses to infants' affective signals. We conclude that NAcc $D_{2/3}$ receptors are involved in maternal responsiveness to affective signals of human infants. $D_{2/3}$ receptors have been associated with maternal responsiveness in nonhuman animals. This evidence supports a similar mechanism in humans and specifies infant-behaviors that activate the maternal dopaminergic system, with implications for social neuroscience, development and psychopathology.

Key words: maternal brain; affect; $D_{2/3}$ receptors; nucleus accumbens; infant behavior; allostasis-regulation

Introduction

Maternal responsiveness and attuned care are imperative for optimal child development and well-being, with major long-term outcomes (Atzil et al., 2018). This is because many physiological processes in the infant are socially regulated by the mother (Atzil et al., 2018). Due to their immature brains, infants cannot independently regulate their own physiology, affect and behavior (Tronick, 1989; Leckman et al., 2004; Atzil et al., 2018). Thus, maternal behaviors are largely aimed at infant care and share a unifying purpose of keeping the infant bio-behaviorally regulated (Atzil et al., 2018). Social regulation of another human is based on social communication. Infants communicate their regulatory changes, often using affective signals, such as smiling, crying or fussing. These affective signals are salient for caregivers (Seifritz et al., 2003; Stein et al., 2010; Wass et al., 2019), potentially because they bare information that is important for the regulation of infants. In turn, accurate recognition of affective signals communicated by the infant enables caregivers to provide attuned care aimed at regulating the infant.

The neural circuits that underlie maternal responsiveness to offspring are mostly studied in rodents (Walker et al., 2004; Numan, 2006). These studies point that individual differences in maternal care are associated with dopaminergic function (Champagne et al., 2004; Numan and Stolzenberg, 2009; Shahrokh et al., 2010). Specifically, micro-dialysis studies in rats demonstrate that mothers secrete dopamine in the nucleus accumbens (NAcc) in response to their pups (Hansen et al., 1993; Champagne et al., 2004; Afonso et al., 2008, 2009, 2011, 2013; Shahrokh et al., 2010). Both D_1 and D_2 receptors have been reported to underlie maternal behavior, although each type is associated with the regulation of different maternal behaviors (Keer and Stern, 1999; Byrnes et al., 2002; Miller and Lonstein, 2005; Parada et al., 2008). While D_1 receptors have been shown to regulate pup licking (Miller and Lonstein, 2005), D_2 receptors are associated with the retention of maternal behavior, and their blockade is associated with the enhancement of nursing behaviors (Keer and Stern, 1999; Byrnes et al., 2002). Both types of receptors are shown to be involved in the consolidation of maternal memory, potentially by enhancing the saliency of pup

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stimulation (Parada et al., 2008). Direct evidence for the involvement of dopamine receptors in human maternal behavior is lacking (Mileva-Seitz et al., 2012), although one study reported that genetic variation in D_2 receptors in mothers is associated with infant-directed vocalizations (Mileva-Seitz et al., 2012). In a different context of social bonding, D_2 receptors in the NAcc—but not D_1—are necessary for the selectivity of partner preference in pair bonds in prairie voles (Wang et al., 1999; Gingrich et al., 2000; Liu and Wang, 2003). Thus, D_2 receptors in the NAcc are suggested to be involved in the selective responses to an attachment partner (Numan and Young, 2016). Evidence from functional magnetic resonance imaging (fMRI) in humans also highlights the NAcc as a central node for maternal responsiveness by repeatedly demonstrating that when mothers observed their infants in the scanner, they showed an increase in blood-oxygen-level-dependent responses in the NAcc (Glocker et al., 2009; Strathearn et al., 2009; Atzil et al., 2011; Kim et al., 2011). Moreover, structural changes in the NAcc were observed in mothers after pregnancy and the transition to motherhood (Hoekzema et al., 2020).

Despite evidence connecting dopamine transmission in the NAcc to maternal responsiveness, it is still unknown which features of the offspring's behavior elicit a dopaminergic response in mothers and whether D_2 receptors are involved in human maternal responsiveness. In this study, we tested the involvement of NAcc D_2 receptors in maternal responsiveness to infant behaviors in human mothers. To do so, we used magnetic resonance-positron emission tomography (MR-PET) neuroimaging and examined the binding of [^{11}C]raclopride, a selective $D_{2/3}$-radiotracer (Farde et al., 1985; Svensson et al., 2019), in the NAcc of mothers while they were watching videos of their infants freely play. We conducted a high-resolution analysis quantifying infants' behaviors during the video and hypothesized that the amount of infants' behavioral signals of affect in the video mothers watched during their scan will determine the level of [^{11}C]raclopride binding in their NAcc.

Method

Nineteen mothers were scanned with a simultaneous MR-PET scanner (Schlemmer et al., 2008; Catana et al., 2013) while watching a video of their own infant playing. We conducted a fine-tuned behavioral analysis on the infant videos and coded infants' affective signals throughout the video. After the initial coding, we quantified the signals: shifting from neutral to positive valence was defined as a positive signal and shifting from neutral to negative valence was defined as a negative signal. This method allowed us to quantitatively measure ongoing affective signals in each video (Figure 1). Then, we assessed maternal free $D_{2/3}$ receptors while watching the video by tracking changes in nondisplaceable binding potential (BPnd) of [^{11}C]raclopride to $D_{2/3}$-type dopamine receptors in the NAcc (Svensson et al., 2019). We calculated the association between changes in [^{11}C]raclopride binding and the number of infant signals mothers observed during the scan.

Participants

Nineteen mothers (age range 21–42 years) and their infants (age range 4–24 months) completed the study. Participants had no psychiatric history and were not breastfeeding nor pregnant. The Massachusetts General Hospital Institutional Review Board approved the study, and all mothers signed an informed consent prior to participating. Analyses are controlled for infants' age. This work follows up on a previous study published in 2017 (Atzil et al., 2017) in the same cohort of mothers, in which we report that mothers who are more attuned to their infants have increased dopamine responses. The results presented here provide a significant step forward by recognizing the specific behaviors of the infants that recruit the dopaminergic system in mothers.

Normality test

Shapiro-Wilk test for Normality was performed on the neural and behavioral variables and was insignificant, suggesting that the variables are normally distributed (left NAcc: $W = 0.929$, $P < 0.173$; Right NAcc: $W = 0.966$, $P < 0.694$; Number of infant signals in the video: $W = 0.959$, $P < 0.543$).

Procedure

The study comprised of a home visit followed by an imaging session. During the home visit, study staff collected video recordings of the infants playing freely. The video was used as the stimulus (Atzil et al., 2011) in an MR-PET scan. While lying in the scanner, mothers passively watched the video of their infants for 10 min prior to the injection of the radiotracer [^{11}C]raclopride, and PET data collection continued for 90 min. Following a 20-min video of the own infant, mothers passively watched a fixation point for 5 min, followed by a 20-min video of the unfamiliar infant (see analysis comparing maternal responses in the own infant condition versus unfamiliar infant condition in Atzil et al. (2017)). During a second scan, mothers watched the same components of the stimuli with the order of the infants reversed. The initial order of the movies was randomized across participants (Atzil et al., 2017).

Combined MR-PET scanner

PET data were acquired using the Siemens BrainPET scanner. This prototype device consists of a head-only PET insert (BrainPET) that fits in the bore of the 3 T TIM Trio MRI scanner (Siemens Healthcare, Erlangen, Germany). Each of the 192 BrainPET detector modules consists of a 12×12 array of $2.5 \times 2.5 \times 20\,mm^3$ lutetium oxyorthosilicate (LSO) crystals readout by a 3×3 array of magnetic field insensitive avalanche photodiodes. A PET-compatible circular polarized (CP) transmit coil and an 8-channel receive array coil were used to acquire the MR data simultaneously.

MRI data acquisition and analysis

Structural data were acquired using a T1-weighted magnet ization-prepared rapid acquisition with a gradient echo sequence (repetition time (TR) = 2530 ms, echo time (TE) = 1.63 ms, inversion time (TI) = 1200 ms, flip angle = 7°, and 1 mm isotropic voxels). MRI data analysis was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) and included unpacking, reconstruction, motion correction, intensity normalization, spatial normalization, white matter segmentation, registration, segmentation, and labeling of cortical and subcortical structures.

PET data acquisition and analysis

[^{11}C]raclopride is a selective $D_{2/3}$ receptor antagonist, primarily used as a PET radioligand to study receptor availability of $D_{2/3}$ in striatal regions (Svensson et al., 2019; Farde et al., 1985). [^{11}C]raclopride was synthesized from the O-desmethyl raclopride precursor and [^{11}C]methyl iodide. The synthesis and subsequent purification by high-performance liquid chromatography were performed according to Farde et al. (1985) with minor modifications. 10.2 ± 1.67 mCi of [^{11}C]raclopride was injected intravenously as a manual bolus for each scan. [^{11}C]raclopride is

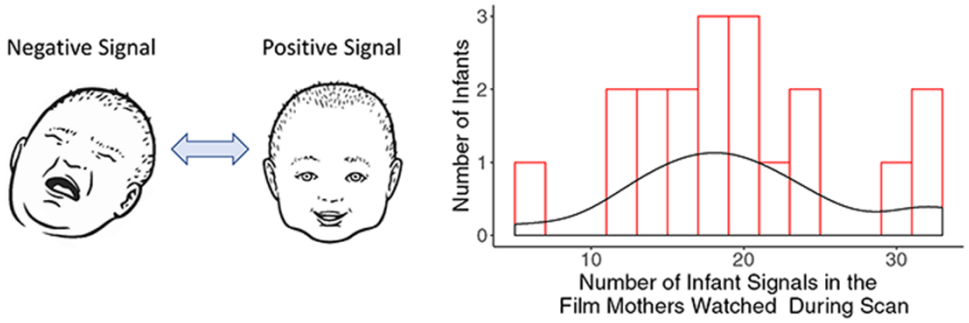

Fig. 1. Using infant behavior to model maternal brain function. We quantified affective signals of infants during free play to test if they recruit the maternal dopaminergic system. Human infants are born helpless in optimizing their own internal milieu, or *Allostasis* (Barrett, 2017), and depend on a dedicated caregiver for on-going regulation of allostasis (Atzil et al., 2018). Accordingly, infants continuously communicate their regulatory requirements using affective signals. Infants communicate negative deviations of allostasis (e.g. pain, hunger, frustration or fatigue) by frowning, fussing or crying. Infants communicate positive changes in allostasis (e.g. soothing, enjoyment and interest) by smiling, laughing and engaging. Thus, infants' affective signals bare information about their allostatic requirements, which is salient for caregivers. In this study, we filmed infants while playing freely, as they spontaneously express affective signals. We applied a high-resolution behavioural analysis, in which we systematically traced the second-by-second infant behavior and quantified the affective signals in each video. Then, mothers observed the same infant video during an MR-PET brain scan. To test the role of maternal dopamine in encoding infant affective signals, we assessed [^{11}C]raclopride binding as a function of how many affective signals each mother observed in her infant video during the scan.

useful to indirectly measure changes in endogenous dopamine response because both compete for binding to $D_{2/3}$ receptors. Thus, an increase in [^{11}C]raclopride binding to the $D_{2/3}$ receptor indexes a proportional decrease in endogenous dopamine transmission (Laruelle, 2000). The BPnd (Innis et al., 2007) of [^{11}C]raclopride was the primary outcome measure of the PET scan. BPnd refers to the radioligand molecules that are specifically attached to a neuroreceptor (as opposed to free radioligand in the tissue) and is the typical measure when using a reference tissue method (Innis et al., 2007). Regional analyses were performed using COMKAT (Muzic and Cornelius, 2001) and a reference tissue model with the time activity curve derived from the cerebellar cortex as a reference (Logan et al., 1996). The cerebellum was chosen as reference region because it does not contain specific $D_{2/3}$ receptor–like binding sites and can be used for the determination of nonspecific binding and free radioligand in the brain (Logan et al., 1996; Salimpoor et al., 2011). [^{11}C]raclopride BPnd was reported to be sensitive to differences in short-term cognitive states between groups, presumably mediated by changes in endogenous dopamine concentration (Yoder et al., 2008). [^{11}C]raclopride BPnd was tested in bilateral NAcc, defined based on FreeSurfer segmentation on the T1-weighted MRIs of all subjects. The NAcc was chosen because both human (Swain et al., 2007; Atzil et al., 2011, 2014, 2017) and nonhuman (Numan, 2006; Lavi-Avnon et al., 2008) research repeatedly reported this region to be central for maternal responsiveness. Moreover, [^{11}C]raclopride BPnd quantification in this region compared to the cerebellum as a reference tissue is reliable (Alakurtti et al., 2015; Svensson et al., 2019). BPnd values in the right and left NAcc for all subjects were imported to SPSS for individual differences analysis testing the association between maternal [^{11}C]raclopride BPnd during the infant's video and the number of infant's signals in the video (Pearson Correlation).

Behavioral coding of infant signals

Human infants constantly sense their allostatic needs and socially communicate them to caregivers (Atzil et al., 2018). Previous literature proposes that experiencing affect represents the mental interpretation of interoceptive allostatic changes ascending from the body (Barrett, 2017; Kleckner et al., 2017). When infants display affective signals, they effectively communicate information about their body budget. For example, frowning, fussing or crying can represent the behavioral display of negative deviations from allostatic regulation as in cases of pain, hunger or discomfort. Smiling, laughing and engaging represent the behavioral display of positive deviations from allostatic balance, such as in cases of soothing, contentment, interest or joy. Thus, the subjective experience of allostatic deviations in the infant can be modeled by tracking the moment-to-moment behavioral display of affect (Barrett, 2017; Kleckner et al., 2017). We conducted a behavioral analysis on videos of infants' free play. Trained coders coded the moment-by-moment shift in infants' valence during the video: Each second was coded as 1 (positive), –1 (negative) or 0 (neutral). Positive signals were defined as shifting from neutral to positive valence. The average number of positive signals across all infant videos was 14.6 times per infant (range: 3–26 times per video). Negative signals were defined as a shift from neutral to negative valence. Negative signals were less frequent, averaged at 5.2 times per infant (range: 0–19 times per video). Inter-rater reliability was conducted for 10% of the videos and averaged 94% of agreement ($k = 0.76$).

Brain and behavior analyses

Infant videos were presented to mothers starting 10 min prior to [^{11}C]raclopride injection, potentially eliciting endogenous dopamine responses. We then injected an intravenous [^{11}C]raclopride bolus to mothers and traced the [^{11}C]raclopride BPnd in each mother following her infant video. To test the association between the individual differences in infant signals in each video and the [^{11}C]raclopride BPnd, Pearson Product Correlations were calculated in SPSS between the amount of affective signals in each infant video during the 10 min prior to [^{11}C]raclopride injection and the following maternal [^{11}C]raclopride binding in the NAcc. Bootstrapping with 5000 iterations was calculated to determine the confidence interval of each association. Negative infant signals were far less common than positive signals. Thus, we assessed the distribution of dopamine responses in mothers to infant videos with primarily positive or primarily negative signals and found no significant difference between [^{11}C]raclopride BPnd in the NAcc during videos with primarily positive or negative signals (see Supplementary Figure S1). Therefore, the quantification of infant signals included both positive and negative signals.

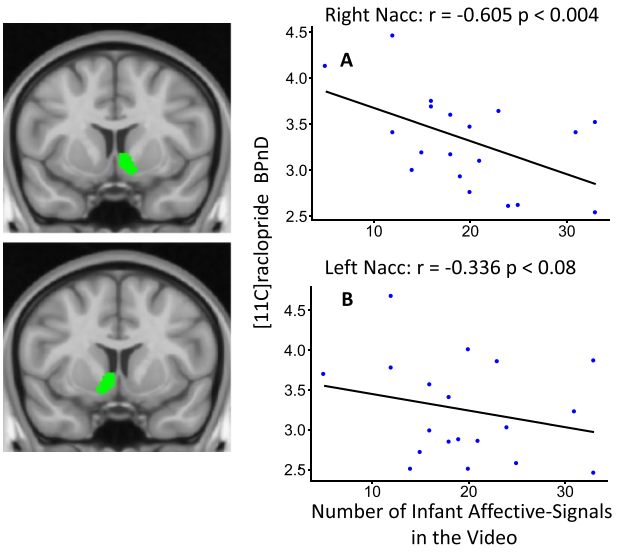

Fig. 2. Increased affective signals of infants during the video is associated with decreased [^{11}C]raclopride specific binding (BPnd) in mothers' right NAcc. The X-axis, depicts the number of affective signals mothers observed in the infant video during her scan. In the Y-axis, [^{11}C]raclopride nondisplaceable binding potential (BPnd) indicates the relative amount of free $D_{2/3}$ receptors. (A) A significant association between infant signals and [^{11}C]raclopride BPnd in the right NAcc: $r = -0.605$, $P < 0.004$, 95% confidence interval = [−0.818, −0.191]. Decreased BPnd indicates that less $D_{2/3}$ receptors were free, possibly due to increased endogenous dopamine response to infant signals. (B) A similar trend is observed in the right NAcc: $r = -0.336$, $P < 0.08$, 95% confidence interval = [−0.674, 0.16].

Results

Results show that [^{11}C]raclopride binding in the NAcc of human mothers is associated with the number of infant signals seen during the scan (Figure 2). One-tailed Pearson Correlation Coefficients were calculated for the association between the number of the infant signals in the video and the [^{11}C]raclopride BPnd in mothers watching the video. The analysis was controlled for infant age. Bonferroni correction was applied to control for multiple hypothesis testing (e.g. left and right NAcc), and bootstrapping (5000 iterations) was applied to determine confidence intervals of the correlation effects. The Pearson Correlation Coefficient between the number of infant signals and [^{11}C]raclopride BPnd in the right NAcc is $r = -0.605$, $P < 0.004$, 95% confidence interval = [−0.818, −0.191]. The Pearson Correlation Coefficient between the number of infant signals and [^{11}C]raclopride BPnd in the left Nacc is $r = -0.336$, $P < 0.08$, 95% confidence interval = [−0.674, 0.16].

Discussion

This study demonstrates that dopamine $D_{2/3}$ receptors in the NAcc are involved in maternal responding to infants: mothers who watched videos with increased infant signals during the scan had less free $D_{2/3}$ receptors in the right NAcc compared to mothers who watched videos with few infant signals. This provides novel evidence that $D_{2/3}$ receptors in the NAcc are involved in human maternal responsiveness. Moreover, these results imply that mothers secrete endogenous dopamine in the NAcc in response to the infants' affective signals.

Previous research has demonstrated that increased dopamine transmission in human mothers is associated with attuned maternal behavior (Atzil et al., 2017). The results presented here advance previous findings by proposing a potential neuro-behavioral mechanism, by which maternal dopamine is sensitive to the affective signals of the offspring and by that promote attuned maternal responding. Monitoring and successfully regulating the basic allostatic requirements of another human requires heightened sensitivity and attention (Atzil et al., 2018). As such, infants' affective signals point to their allostatic state and are thus extremely salient for caregivers, potentially stimulating dopamine secretion in mothers' NAcc. Maternal sensitivity to their infants' affective signals potentially enables mothers attuned responding to the infant's needs, which enables efficient social regulation. The inhibitory function of D_2 receptors is suggested to be essential for selective behavioral reactivity by gating strong and salient sensory input (Nicola et al., 2000) that allows accurate behavioral responsiveness. The results emphasize the relevance of allostasis and co-regulation as mechanisms of mother–infant bonding.

The study includes a relatively small cohort of mothers (19). While numerous fMRI studies focus on reward circuitry in a social context, actual measurement of the dopaminergic system in human mothers is rare, hard-to-attain and involves smaller cohorts of subjects. Yet, this research complements human fMRI studies and nonhuman neurotransmission studies, adding highly novel and significant knowledge on the neural transmission of dopamine during social brain processing in humans. Moreover, the findings of this study, linking infants' affective signals to maternal $D_{2/3}$ receptors in the right NAcc, show a strong effect size and robust statistical significance, thus suggested to be reliable. Future studies are needed to replicate this finding in larger cohorts, also assessing other factors in mothers and infants that can affect dopamine transmission, such as age, relationship status, and other sociodemographic parameters.

Our approach utilizes a high-resolution behavioral analysis, applied to the scan *stimulus* to understand which aspect of the infant's behavior triggers maternal brain response. Using this approach, we were able to associate maternal dopaminergic responses to specific infant behaviors. Importantly, this research evaluates maternal dopaminergic responses to ecological valid infant signals that are spontaneously communicated during free play of the infant.

Interestingly, there were no differences between the dopaminergic responses to infants' positive and negative affect. The lack of valence specificity suggests that dopamine is involved in processing salient information rather than positive rewards. For mothers, both positive and negative infant signals are salient because both bare information about the infant's allostasis and are thus important for the provision of attuned maternal behavior. Similar dopaminergic responses to positive or negative infant signals is in line with previous evidence showing that dopaminergic neurons encode salient stimuli that require attention rather than rewarding or 'hedonic' events of positive valence (Schultz, 1994; Schultz et al., 1997; Berridge and Robinson, 1998; Horvitz, 2000; Zink et al., 2004). Moreover, fMRI studies in humans show increased responses in mothers' NAcc to both positive and negative infant signals (Strathearn et al., 2009; Kim et al., 2011).

Human and nonhuman animal research establishes that dopamine supports maternal responding to infants, yet this mechanism is not specific to social responding. In rats, postpartum hormones reduce the baseline levels of dopamine and by that increase the dopaminergic sensitivity to pup stimuli (Afonso et al., 2009). However, food is also salient for mother rats (Afonso et al., 2013) and elicits a behavioral response and a corresponding dopamine response (Afonso et al., 2009). In humans, previous studies using similar methodology found reduced [^{11}C]raclopride

binding, in the ventral striatum, indicating increased dopamine responses to music (Salimpoor et al., 2011), to monetary rewards (Jonasson et al., 2014) and to food (Small et al., 2003). Like social stimuli, all three are relevant for allostasis in the sense that they can elicit a behavioral response that is required to obtain a reward (or 'effort') (Montague et al., 2004; Salamone et al., 2007; Floresco et al., 2008; Phillips et al., 2008). These studies support the idea that maternal behavior is supported by domain-general neural circuits that underlie motivated behavior and not by a dedicated social system.

This study suggests that dopamine is involved in encoding affect in other humans. Future studies are warranted to mechanistically test the role of dopamine in the recognition and regulation of affect and allostasis in the mother–infant dyad, as well as in other human bonds. Linking maternal $D_{2/3}$ receptors in the NAcc to infant regulation has implications for basic and clinical research. This is of particular interest in the context of impaired social bonding, such as in cases of postpartum depression and autistic spectrum disorders, where maternal responsiveness is impaired (Beck, 1995; Rutgers et al., 2004) and may thus benefit from behavioral and pharmacological interventions that target the social regulation of allostasis and $D_{2/3}$ receptors in order to improve maternal responsiveness and child well-being.

Conclusion

Here, we aim to model ecologically valid aspects of social responding in a neuroimaging setting to understand the role of dopamine transmissions in mothers' NAcc in encoding affective signals of infants. We demonstrate in human mothers that the occupancy of $D_{2/3}$ receptors is sensitive to affective signals spontaneously communicated by infants during the scan. This work points to a dopaminergic role in encoding the partner's behavior during social interaction and sheds light on the neural and behavioral processes that underlie social interactions in humans and the involvement of striatal dopamine in it.

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest

None declared.

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