Gene-environment interaction influences attachment-like style in mice

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Attachment styles are established soon after birth and form the basis for a healthy psychological life during adulthood. Here, we investigated whether genetic background (i.e. isogenic strains: C57BL/6N and BALB/c) and parent-of-origin (i.e. reciprocal hybrids) epigenetic effects influence attachment-like styles in mice. We discovered that a specific genetic and epigenetic assortment exerts a role on the development of a secure or insecure attachment-like style. In particular, when biological mothers raise their pups, the attachment-like style is mainly secure, independently of the genetic background. However, when foster mothers raise pups, the attachment-like style can be either secure or insecure, depending on the particular genetic background, and this effect is paternally transmitted. Finally, we observed that secure attachment-like in mice leads to greater sociability during adulthood, while insecure attachment-like leads to reduced sociability. Our study sheds light on gene-environment interactions that shape the attachment-like style early in development and pave the way for a healthy psychological life.

Keywords: Attachment, fostering, mice, parent-of-origin, social behavior

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Mammals are mostly altricial animals, which means that they can survive only if adequate parental care is provided after birth. Attachment is the bonding behavior of an infant toward the main caregiver. The type of relationship between immature offspring and caregivers, known as attachment style, paves the way for psychological life in adulthood. Securely attached infants rely on their primary caregiver as a secure base and develop autonomy, a positive self-image and the ability to form emotionally close relationships (Bucci et al. 2016). Insecure attachment is developed when the caregiver is inconsistent and does not respond to the infant’s needs.

The consequences of dysfunctional attachment styles vary and can be disastrous, adversely affecting adult personality, security, emotionality and sociability (Bremner 2003; Heim & Nemeroff 2001; Landers & Sullivan 2012; Sheinbaum et al. 2015; Sullivan 2012). Personality disorders have a profound impact on our society, creating a considerable economic burden for national health services and reducing productivity worldwide (Tyrer et al. 2010).

Here, we studied mice as a model for understanding the genetic and epigenetic components that establish attachment styles early in life and the consequences of this attachment in adulthood. In particular, we investigated whether specific parent-of-origin epigenetic mechanisms, e.g. in genomic imprinting, affect attachment behaviors. Genomic imprinting is an epigenetic phenomenon in which maternal and paternal alleles are not functionally equivalent (Bartolomei & Ferguson-Smith 2011). We tested maternal and paternal allelic combinations in setting behavioral responses with a focus on specific genetic effects and environmental factors such as early foster parenthood.

The behavioral premises of our investigation were based on the different mothering styles of two common inbred strains: BALB/c and C57BL/6N. Whilst the latter dams are recognized as ‘good mothers’, BALB/c dams are reported to spend less time licking their pups and show less arch-backed nursing (Calatayud et al. 2004; Pribe et al. 2005; Tarantino et al. 2011). The genetic premises of the experimental design were the isogenic backgrounds of the two inbred strains and potential parent-of-origin effects that can emerge in their reciprocal hybrids (Islés et al. 2001; Lawson et al. 2013). Indeed, the first-generation (F1) offspring of the two strains always presents the same complement of heterozygous individuals regardless of parental assortment. However, when there is an underlying parent-of-origin regulatory process, phenotypic differences between reciprocal crosses can be observed as a consequence of a particular parental assortment. Therefore, along with cohorts of C57BL/6N and BALB/c mice, we studied litters of C57BL/6N and BALB/c reciprocal hybrids.

To isolate the effect of maternal care (environmental) from parent-of-origin (genomic imprinting) effects, we conducted a parallel investigation on the same four groups (C57BL/6N, BALB/c, F1 and F1r; Fig. 1a) that were raised by unrelated foster CD1 mothers.

To assess attachment behaviors in 1-year-old infants, Ainsworth devised the strange situation procedure (SSP) (Ainsworth et al. 1978), a behavioral test based on the natural tendency of infants to attach to caregivers, preferentially the mother. In the SSP, the exploratory and social behavior of the infant is recorded in a room during various short episodes during which the infant is in the presence of the
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**MOUSE STRANGE SITUATION PROCEDURE**

Pre-test: familiarization between the mother and the stranger. Test episode 1: mother, pup and stranger are introduced in the arena. Test episode 2: pup and stranger are left alone in the arena. Test episode 3: the mother returns to the arena.

mother and/or a stranger. Briefly, after an assessment of the styles of interaction between the mother and the infant, the experiment assesses the response of the infant in presence of an unknown woman along with the mother and then in the presence of the stranger alone. At this point, the mother returns while the stranger leaves the room, and then the infant is left alone. The stranger then returns, and then the mother returns before the stranger leaves for good. Many psychological factors are taken into account as the infant goes through a total of eight situational episodes. However, the primary objective of this assessment is to determine the attachment style based on (1) the interest shown by the child toward the stranger and (2) the behavior of seeking comfort from the mother once infant and mother are reunited. The main outcome of this assessment is that the attachment style is categorized as either secure or insecure (Ainsworth et al. 1978; Sheinbaum et al. 2015). Secure attachment is represented by the active exploration of the stranger, especially when the mother is in the room, and then by seeking consolation from the mother when she returns. Attachment is interpreted as insecure when the infant avoids the stranger and then shows either avoidance or indifference toward the mother when she returns to the room. We modified the SSP to study the attachment-like behavior in mouse pups. We could not faithfully mimic the SSP on account of objective specie-specific issues and the need to minimize stress on both the mother and the pups.

The results of our study show important genetic and gene-environment effects in determining particular attachment-like styles and adult behavioral traits.
The total number of animals tested was 140. We tested two litters for each genotype. Each litter size was either 6 or 10; 64 pups were fostered while 76 were raised by their biological mothers.

Materials and methods

Animal husbandry
C57BL/6N and BALB/c mice were imported from Charles River (Italy). Then at the Istituto Italiano di Tecnologia (IIT) mice were bred in order to obtain two cohorts of first generations (F1s) mice derived from intercrosses within each strain; yet, two additional cohorts of mice, F1 and F1r (reciprocal), were obtained from the reciprocal hybrids from C57BL/6N and BALB/c inbred strains. All strains were housed at a constant environmental temperature of 23°C, under a 12:12 light/dark cycle with lights on at 0800 h until 2000 h with food and water available ad libitum.

Animals were mated by introducing the female into the male cage and monitored for 1 h; then the mice were checked daily every morning and evening. Between E16 and E18 the dam was allocated an individual cage with paper for nesting. All dams were primiparae and both females and males were 12–15 weeks old when mated. Litters that were fostered were removed from their cage at birth, in the morning of P0, and smeared with sawdust from the cage of a lactating CD1 to which they were allocated. Animals were mated by introducing the female into the male cage and monitored for 1 h; then the mice were checked daily every morning and evening. Between E16 and E18 the dam was allocated an individual cage with paper for nesting. All dams were primiparae and both females and males were 12–15 weeks old when mated. Litters that were fostered were removed from their cage at birth, in the morning of P0, and smeared with sawdust from the cage of a lactating CD1 to which they were allocated. Cages were changed at weaning at P28 and every 2 weeks thereafter.

For each experimental condition we tested each pup of two litters (see Table 1). A total of 140 animals were tested; the size of the 2 litters was 10 and 6, respectively, for each genotype of the fostered litter. For all litters raised by their biological mother the litter size was 10 but for 1 F1 litter that had 6 pups. Only 1 pup of a litter of the foster condition had to be culled to downsize the litter to 10. All animal procedures were approved by the ethical national committee in Italy, for IIT Genova. The study followed ARRIVE guidelines (http://www.nc3rs.org.uk/arrive-guidelines).

Mouse strange situation procedure
In mice, to overcome species-specific differences, we devised a stranger effect. In the third and final episodes, the mother was returned to the arena with the mother and the stranger. In the second episode, the mother's nipple; after testing their tail was carefully colored with a sex-matched virgin C57BL/6J, to each other. For the stranger we have chosen a different strain background to avoid effects due to the same strain. Several behavioral, cardiovascular and chemical phenotypic differences between C57BL/6J and C57BL/6N have been documented (Matsuo et al. 2010; Simon et al. 2013). Between pups the arena was thoroughly cleaned with water. All MSSPs were video recorded with a webcam and scored offline, for each episode of each mouse of each litter. Altogether 420 episodes, 3 per pup, were scored; for each episode we quantified the time (seconds) spent by the pup actively exploring (sniffing and touching) the stranger (tS1) and the mother (tM1) (Fig. 2).

Social interaction test
For this test we habituated each mouse (at 8 weeks of age) to the arena (60 × 60 × 60 cm³) at P18. The pretest was conducted to habituate the dam and the stranger, an age- and sex-matched virgin C57BL/6J, to each other. For the stranger we have chosen a different strain background to avoid effects due to the same strain. Several behavioral, cardiovascular and chemical phenotypic differences between C57BL/6J and C57BL/6N have been documented (Matsuo et al. 2010; Simon et al. 2013). Between pups the arena was thoroughly cleaned with water. All MSSPs were video recorded with a webcam and scored offline, for each episode of each mouse of each litter. Altogether 420 episodes, 3 per pup, were scored; for each episode we quantified the time (seconds) spent by the pup actively exploring (sniffing and touching) the stranger (tS1) and the mother (tM1) (Fig. 2).

Statistical analysis
The unit of observation of this study was the single pup. The pups were grouped according to their genotype (four in total: C57BL/6N, C57Bl/6J, F1, F1r and BALB/c) and to the maternal breeding (biological or foster). We used the paired two tails t-test for comparisons between t(M1) and t(S1) to assess ‘maternal preference’ and for comparisons between t(M1) and t(L1) to assess the ‘reunion’, within each group. We run repeated-measures one-way ANOVAs for the comparison of t(S1–3) for the ‘stranger effect’, followed by post hoc analysis using the Newman–Keuls multiple comparison test. In addition, we have run two one-way ANOVAs, one to test the mean difference (tM1 – tS1) and the other to test the mean difference (tM1 – tL1) across strains for each condition (biological and foster mother). Finally, for the social interaction test analysis, we used paired two tails t-tests for comparisons between t(E1) and t(E2) within each experimental group and a one-way ANOVA to test the mean difference (t(E1) – t(E2)) across strains for each condition.

Results
In our study, we propose a modified version of the classical eight-episode human SSP, called the mouse SSP, the MSSP (see Materials and methods and Fig. 1b).
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**Maternal preference is paternally driven**

All pups in the first experiment, which were raised by their biological mothers, showed a significant ‘maternal preference’ effect (C57BL/6N: $t_{159} = 8.36$, $P$-value < 0.001; F1: $t_{159} = 4.11$, $P$-value < 0.001; F1r: $t_{159} = 4.70$, $P$-value < 0.001; BALB/c: $t_{159} = 2.43$, $P$-value = 0.025; Fig. 2a). In the second experiment, in which foster mothers raised the mice, C57BL/6N mice presented a ‘maternal preference’ effect, whereas BALB/c mice did not (C57BL/6N: $t_{159} = 8.88$, $P$-value < 0.001; Fig. 2d). Furthermore, the two hybrid cohorts expressed a behavioral response that was consistent with paternal inheritance. In particular, F1r mice that had C57BL/6N fathers showed a ‘maternal preference’ effect ($t_{159} = 5.94$, $P$-value < 0.001), while F1 mice that had BALB/c fathers showed no ‘maternal preference’ effect. This result provides evidence of the role of gene-environment interaction in the response to mother-pup separation. However, the behavioral response for this trait is paternally driven. Overall the mean difference of time spent exploring the mother with the time spent exploring the stranger across strains was significant ($F_{3,60} = 4.40$, $P$-value = 0.007; $F_{3,60} = 18.67$, $P$-value < 0.001; see Table S2). The post hoc tests showed only a significant difference, for the pups raised by their biological mothers, between the C57BL/6N and BALB/c mice ($P$-value < 0.01). For the fostered pups, the only non-significant differences were between C57BL/6N and F1r and between BALB/c and F1 mice (all significant differences $P$-values < 0.001; see Table S2).

**Reunion effect with the mother is paternally driven**

In the analysis of the second behavioral response, the ‘reunion’, we observed in the first experiment a positive rebound effect (i.e. the pup spent more time exploring the mother with the time spent exploring the stranger during episode 3 ($t_{M3}$) than during the other two episodes ($t_{S1}$ and $t_{S3}$)).

**Supporting Information**

- **Tables S1 and S2**
- **Figure 2**
mother during episode 3 than during episode 1) in C57BL/6N mice ($t_{15}=8.84$, $P$-value < 0.001) but not in BALB/c mice (Fig. 2b). However, F1 mice with C57BL/6N mothers exhibited rebound explorations during the reunion ($t_{15}=5.68$, $P$-value < 0.001), while F1r mice with BALB/c mothers had no rebound (Fig. 2b). This finding indicated a maternal influence on the rebound measure. In the second experiment, where the effect of maternal care was standardized across all mice, the parental strains maintained the same differences as for the first experiment. In particular, we observed a rebound effect in C57BL/6N mice ($t_{15}=4.85$, $P$-value < 0.001) but not in BALB/c mice (Fig. 2e). However, in this experiment, the fostering factor across all groups led to differences in the behavioral responses of F1s. Specifically, while F1r mice expressed rebound behavior during the reunion with the mother ($t_{15}=5.05$, $P$-value < 0.001), similar to C57BL/6N mice, F1 mice did not, indicating a paternal effect. The results for the ‘reunion’ phenotype showed an additional gene-environment interaction. Interestingly, in the first experiment the good maternal care of the C57BL/6N dams interacted with the paternally driven attachment-like style to enhance the maternal preference in the F1 mice (i.e. the ‘reunion’), while the F1r mice raised by BALB/c mothers did not exhibit this behavior. Overall the mean difference of time spent exploring the mother with the time spent exploring the stranger across strains was significant ($F_{3,72}=9.30$, $P$-value < 0.001; $F_{3,60}=7.01$, $P$-value < 0.001). The post hoc tests showed significant differences, for the pups

Figure 3: Social interaction in mice. (a) Here, we represent the social test in which each mouse is exposed to two conspecific strangers in the arena, each encounter lasts 1 min with an interval of 3 min. Experiment 1 (b) represents the behavior of mice raised by their biological mother, while experiment 2 (c) represents the behavior of mice raised by a foster mother. When the explorations of conspecific strangers ($t(Ei)$) are similar between the two episodes, the effect is represented by a gray circle. If the exploration decreases in episode 2, the effect is represented by an open circle. The groups are 'A' = C57BL/6N; 'B' = BALB/cX C57BL/6N F1r; 'C' = C57BL/6NxBALB/c F1 and 'D' = BALB/c. All data are reported as percentages of time spent exploring during the two trials for each group. Graphs are presented as the means ± SEM. Significant differences are indicated as follows: * $P$-value < 0.05.
raised by their biological mothers, between: C57BL/6N and BALB/c (P-value < 0.05), F1r and F1 (P-value < 0.001), F1r and C57BL/6N (P-value < 0.001), and F1 and BALB/c (P-value < 0.01). For the fostered pups the post hoc tests showed significant differences between C57BL/6N and BALB/c (P-value < 0.01), F1 and C57BL/6N (P-value < 0.05), F1r and F1 (P-value < 0.05), F1r and BALB/c (P-value < 0.001) (see Table S2).

Exploration of the stranger is paternally driven
In the first experiment, all groups showed a significant ‘stranger effect’, represented by increased exploration of the stranger by the pup in episode 2 (C57BL/6N: P-value < 0.001; F1: P-value < 0.001; F1r: P-value = 0.02; BALB/c: P-value = 0.006; Fig. 2c). Instead, in experiment 2, the behavioral response of the mice was expressed through paternal inheritance (C57BL/6N: P-value < 0.001; F1: P-value = 0.058; F1r: P-value = 0.007; BALB/c: P-value = 0.900; Fig. 2f). In particular, only C57BL/6N and F1r mice showed an increased exploration of the stranger, while BALB/c and F1 mice did not show a ‘stranger effect’. Once again, the good C57BL/6N maternal care in the first experiment masked the paternally driven effect.

Attachment-like styles predict adult social interaction
Early life experiences have important effects across the life span of an individual (Roth & Sweatt 2011). Various clinical approaches have suggested that adult psychological life is often an expression of the attachment style during infancy (Sheinbaum et al. 2015). In addition, long-term studies have shown that a particular attachment style in humans is relatively stable from infancy to early adulthood (Waters et al. 2000). Therefore, we tested the social interactions of the same mice for which we had characterized attachment-like styles. Standard social behavioral testing in mice includes either the exploration of conspecifics across different spatial conditions or repeated exposures to the same animal. In order to avoid the burden of long and repeated behavioral procedures, we simplified our study by exposing each mouse to only two trials and with two different mice. Because of the novelty of the conspecifics at each trial a normal mouse is spontaneously motivated to interact with each conspecific. In the assessment of social behavior, we measured the time each mouse (now at 8 weeks of age) spent exploring their reunion; seeking for the mother in the human version of the test testifies the secure attachment of the infant (Ainsworth et al. 1978; Sheinbaum et al. 2015). Therefore, while most pups raised by their biological mothers showed signs of secure attachment-like, pups raised by foster mothers showed either secure or insecure attachment-like behaviors according to their genotype. Furthermore, we observed that when foster mothers raised their pups, all behavioral responses to define specific attachment-like styles were paternally driven, with secure attachment-like occurring in the offspring of C57BL/6N fathers, while insecure attachment-like occurred in the offspring of BALB/c fathers. A limitation of this study is that we did not monitor the stress-response system in the partners of the dyad when they were assessed; further studies could assess, e.g. the plasma cortisol level in pups and mothers before and after the MSSPs. Moreover, further studies in the future should be dedicated to investigate additional effects because of the genetic background as specific paternally driven effects differentially influence the development of attachment-like behaviors in mice. Interestingly, it has been observed in other rodents, such as guinea pigs, that pups prefer being in proximity of the mothers rather than other adults (Hennessy et al. 2003) although they would also explore other female adult conspecific (Graves & Hennessy 2000) and the presence of the mother is more effective in lowering stress levels, compared with other female adults, when the pup is placed in a novel environment. Attachment has been also widely explored, in the rat, by Regina Sullivan’s group. Her group has described the neurobiology of attachment and assigned a primary role to the amygdala (Sullivan et al. 2000). They showed that attachment occurs even with trauma and/or an abusive caregiver; in fact they found that the presence of the dam suppressed the pup’s response to a threat or an aversive learning (Perry & Sullivan 2014; Shionoya et al. 2007) thus allowing the young individual to survive although with long-term psychological effects that may become evident with maturation.

Imprinted genes, such as Peg3, Mest, Gnas and Gnasxl, play a pivotal role in many aspects of maternal behavior (Isles & Holland 2005); however, a direct effect of an imprinted gene on the development of attachment behavior has not been determined. The intragenomic conflict theory of genomic imprinting advocates for a particular role for paternally imprinted genes (Haig 2014; Haig & Wilkins 2000). Paternally expressed genes are thought to maximize the allocation of resources to the pups, while maternally expressed genes are thought to lead to an equal distribution among the offspring. The evolutionary explanation for this difference resides in greater maternal than paternal relatedness among

Discussion
Taken together, the behaviors of our mice led us to define different attachment-like styles according to genetic, epigenetic and environmental differences. In particular, we observed that C57BL/6N mice presented all three behavioral markers (i.e. maternal preference, reunion and stranger effect) of a secure attachment-like style, whereas BALB/c mice showed only two of the three positive markers. The latter group did not exhibit rebound exploration of BALB/c during their reunion; seeking for the mother in the human version of the test testifies the secure attachment of the infant (Ainsworth et al. 1978; Sheinbaum et al. 2015). Therefore, while most pups raised by their biological mothers showed signs of secure attachment-like, pups raised by foster mothers showed either secure or insecure attachment-like behaviors according to their genotype. Furthermore, we observed that when foster mothers raised their pups, all behavioral responses to define specific attachment-like styles were paternally driven, with secure attachment-like occurring in the offspring of C57BL/6N fathers, while insecure attachment-like occurred in the offspring of BALB/c fathers. A limitation of this study is that we did not monitor the stress-response system in the partners of the dyad when they were assessed; further studies could assess, e.g. the plasma cortisol level in pups and mothers before and after the MSSPs. Moreover, further studies in the future should be dedicated to investigate additional effects because of the genetic background as specific paternally driven effects differentially influence the development of attachment-like behaviors in mice.
developing pups. Consequently, the expression of a gene according to parental origin may promote the exploitation of maternal resources by the pup (or infant). In fact, while the key role of the mother is to provide nutrients, prenatally (Reik et al. 2003) and perinatally (Plagge et al. 2004), in the postnatal period it becomes pivotally important to promote positive signals in the sensory system of the mother (Wilkinson et al. 2007). The results of this study also converge with the coadaptation theory of genomic imprinting (Cowley et al. 2014; Wolf & Hager 2006), in which allele matching between the mother and the pup reinforces the relationship between the infant and the mother.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher’s web-site:

Table S1. The t-values, degrees of freedom and P-values for each genotype and mothers condition.

Table S2. The F-values, degrees of freedom and P-values for each genotype and mothers condition.