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Simulated viral infection in early-life alters brain morphology, activity and behavior in zebra finches (*Taeniopygia guttata*)

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ABSTRACT

Early-life immune challenges (ELIC) have long-term effects on adult behavior and brain development. ELIC studies on birds are still few, but they are epidemiologically crucial since birds are important hosts of many mosquito-borne viruses. In this study, we administered a viral infection mimicking agent, Polyinosinic: polycytidylic acid (Poly I:C), to nestling zebra finches on post-hatch day 14. When birds became sexually mature, their general activity (i.e., hopping, feeding behavior) and mosquito defense behaviors (i.e., hops, head movements, pecks, wing movements, foot movements, and scratches) were measured. Following behavioral trials, brains of male birds were collected for anatomical and histochemical analyses. Poly I:C challenge had sex-dependent effects on general activity and mosquito defense behaviors. When compared to control females, Poly I:C challenged females hopped and fed less often in their general activities, but hopped more often in the presence of mosquitoes. Poly I:C challenged males did not differ from control males in any behaviors. Brain analysis revealed that the nucleus taeniae of the amygdala (TnA) of Poly I:C challenged males were smaller in volume yet had more neurons expressing immediate-early gene proteins compared with controls, suggesting a more active TnA. These results suggest that immune challenges early in the life could have long-term effects on behaviors and brains of zebra finches, which may influence disease spread and fitness of individual birds.

1. Introduction

Early life immune challenges (ELIC) can have long-term effects on adult behaviors [8,42,67]. In mammals, for example, ELIC caused increased anxiety [31], memory deficiencies [81], and abnormal social behaviors [7]. These studies suggested a possible link between ELICs and neurodevelopmental disorders including mental and cognitive abnormalities [92]. In birds, there are few studies that have investigated effects of ELIC on neural development [42]. However, studies in birds are important as adult birds are primary hosts of many parasites including mosquito-borne viruses [106] such as West Nile virus. It is therefore important to understand whether early-life exposure to these same viruses could have long-term effects on an individual's role in disease dynamics by altering their adult behavioral competency [6].

Viral ELIC may represent an important source of ELIC in natural populations because young animals are naturally susceptible to viruses through mosquito bites. Nestling birds are especially vulnerable since they lack full feather coverage and effective defensive behaviors [57].In the present study, we used polyinosinic: polycytidylic acid (Poly I:C) as an immune challenging agent to investigate how early-life exposure to viral diseases could affect avian behavior in adulthood. Poly I:C is a double-stranded RNA analog and mimics the acute phase response to viral infection [26,67]. Poly I:C affects sensorimotor [109,115] and social behaviors [1,9,61] in mammals. Poly I:C injections in one-day-old domesticated chicks (*Gallus gallus)* caused memory deficiencies in passive avoidance tasks just after Poly I:C exposure (Kent et al., 2007). However, long-term studies on effects of Poly I:C as ELIC are lacking in birds.

ELIC's effects on adult behavior could have several implications for disease dynamics [6,40,64] by modifying bird response to questing vectors. In general, the activity of a bird significantly affects the rate of mosquito bites [28]. In laboratory studies, mosquitoes were less likely to bite more active zebra finches compared with less active finches [40]. Also, defensive behaviors that are directed to mosquitoes, such as

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head movements, wing movements, and hopping decreased the number of bites [27,34]. For example, in quail (*Coturnix japonica)*, the intensity of defensive behaviors was negatively correlated with the number of blood-fed mosquitoes [2,3]. These studies suggest that if an ELIC affects the activity of a bird, it would eventually change the rate of mosquito bites. To test this hypothesis in the current study we observed activities of birds in both the absence and presence of mosquitoes.

ELIC also affects the brain development of vertebrates [8,10,50,66]. In particular, Poly I:C injection to pregnant rats (*Rattus norvegicus*) reduced the volume of the amygdala in offspring [25]. Although it is still in debate regarding the avian equivalent of the mammalian amygdala, the nucleus taeniae of the amygdala (TnA) is well established as a homologue to part of the mammalian amygdala, the medial portion in particular[83,112]. Similar to the mammalian medial amygdala, the avian TnA is involved in social and/or sexual behaviors according to lesion studies [20,48,99]. In the present study, we investigated Poly I:C effects on the TnA volume to see whether the avian brain would also be affected by ELIC similar to the mammalian data. Any changes in neural structure volume may suggest changes in the number of neurons or complexity of neural connections, implying effects on neural activity and behaviors relevant to the structure in question. Thus, in addition to the volume measurement, we investigated changes in sexual behaviors previously linked to the TnA [18,48].

We also investigated neuronal activity in TnA by counting the neurons expressing immediate early gene (IEG) proteins. IEGs, such as c-fos and c-jun, are sets of transcription factors that can be induced by external stimulation [72]. In the avian brain research, one type of IEG, *zenk* and its protein ZENK, have been successfully used to study neuronal activity of different structures [77]. Comparing the number of ZENK expressing neurons in different conditions gives information on the possible roles of brain regions of interest. ZENK expression in TnA is known to be correlated to changes in social and/or sexual behaviors [18,97]. In the current study, a comparison of ZENK expressing neurons in TnA of normally developed and immune challenged finches would be an insightful index of how brain activity and behavioral output might be affected by ELIC.

In order to test the long-term effects of Poly I:C as an immune challenge agent on behavior and brain development, we injected both male and female nestling zebra finches with Poly I:C on post-hatch day (PD) 14. When finches became sexually mature, we observed their general activity during periods when they would naturally be fed upon by many mosquito species [103]. Zebra finches were then exposed to southern house mosquitoes (*Culex quinquefasciatus*) to measure their mosquito defense behaviors directly. In order to study Poly I:C's effects on sexual behaviors and the associated brain region TnA, male zebra finches were placed next to a novel female finch to trigger courtship behaviors and induce IEG expression [18] before their brains were collected for volume and neural activity analysis. We predicted that Poly I:C challenged birds would be less active, as was previously found in mammals [67]. We predicted smaller and less neuronally active TnAs in Poly I:C challenged males than controls as adverse early life environment is known to negatively affect development of bird brains [46,94].

2. Methods

2.1. Animals

2.1.1. Breeding colony

Thirty-six (36) adult zebra finches (18 females and 18 males) were purchased from local breeders across the Tampa Bay, FL, area. They were housed in flight cages (90w X 51 h X 51d cm), each of which contained three males and three females in the College of Medicine, University of South Florida. Birds were kept on a 12 h light: 12 h dark cycle and given ad libitum standard diet of seed (ABBA1900 exotic finch food and millet, ABBA Products Corp., Hillside, NJ), water, and cuttlebone. Birds were also provided with fresh greens, wicker nest baskets, and nesting material to stimulate breeding. Nests were checked daily for eggs. All procedures were in accordance with NIH guidelines and approved by the University of South Florida Institutional Animal Care and Use Committee (protocol number IS0000721).

2.1.2. Mosquito husbandry

Mosquitoes used in behavioral assays were from a laboratory colony of *Culex quinquefasciatus* Say established from wild-caught females from Indian River County, FL (generation > F75) [84]. Female mosquitoes were fed on live, restrained chickens (University of Florida IACUC #201507682) to maintain colonies. The progeny of three to four females (approximately 600 eggs total) were placed in plastic rearing pans (45.7 cm × 53.3 cm × 7.62 cm) containing approximately 3 L water and larvae were reared at 28 °C under a 14:10 (light: dark) cycle. Each pan received 1:1 Brewer's yeast and lactalbumin daily (20 mg/mL) as larval food. Pupae were transferred to plastic containers with ~200 mL of clean tap water and placed into cages (30.48 cm3) for adult emergence. Adults were provided 20% sucrose water ad libitum. Twenty-four hours prior to exposure to zebra finches, sucrose water was removed, and adult females were transferred to one-liter cardboard holding cages with mesh screen tops. Mosquitoes of uniform age (4 days post-emergence) were used in all trials.

2.1.3. Early-life-immune challenge

Fourteen (14) male and 19 female zebra finches that hatched in the colony were used in our experiment. Birds were grouped into two cohorts depending on hatch date. On PD 14, siblings in each nest were randomly assigned to either the Control (16 birds) or immune-challenged (Poly) (17 birds) group. Birds in the Control group were injected subcutaneously in their pectoral muscle with 100 μL of 0.9% saline solution whereas those in the Poly group were injected with Poly I:C (25 mg/kg body mass) in 100 μL 0.9% saline solution [23]. On ~PD30, fledged nestlings were transferred to another flight cage (6 birds per cage) in the Department of Psychology animal facility where behavioral trials were performed. Birds were semi-randomly placed to the flight cages balancing sex and treatment of birds in the cage. When the birds reached 4–6 months old, behavioral trials started.

2.2. Behavioral trials

The behavior of all 33 male and female birds were observed during general activities and mosquito exposure trials. Only 14 male zebra finches were further used for the novel female exposure trials by placing male birds next to a novel female for an hour. Novel female finches were purchased from local breeders in Tampa Bay area and were housed in a separate room throughout the experiment with no treatment.

2.2.1. General activities

A week before general activity observations, birds were placed and held singly in their own cages (56w X 56d X 45 h cm) in the housing room lit with full-spectrum fluorescent bulbs with UV (Reptisun, Zoo Med). Each cage contained a food cup, water cup, and two perches separated by 15 cm. In this room, birds could see and hear birds in other cages. The natural behaviors of birds were recorded with cameras (Foscam, FI9821W) that were connected to a laptop computer (HP G71) outside of the room. Recording occurred for 15 min twice a day – immediately after lights-on each morning and just before lights-off each evening– for three consecutive days. Videos were scored using JWatcher™ 1.0 [11], recording the number of hops on perches, number of food cup visits, and number of pecks at food (following Careau et al. [19].

2.2.2. Mosquito exposure

Fifteen minutes before mosquito exposure, zebra finches were

placed alone into a mosquito-proof cage (30w X 30 h X 30d cm). In each cage, there were two 45 cm long diagonal perches, 10 cm and 20 cm above the ground, respectively. There was also a water dish in the cage. An observation camera (Foscam, FI9821W) was placed 30 cm front of the cage and connected to PC (Dell, Optiflex 7010). The room was lit with full-spectrum fluorescent bulbs with UV (Reptisun, Zoo Med). After 15 min of habituation, female mosquitoes (mean = 32 ± 7 per cage, minimum 20, maximum 44) were introduced into the cage through one wall with a closeable mesh opening. Female mosquitoes were held in one-liter cardboard containers with mesh screen tops until introduction to the cage. Once the cardboard was fully inside the cage the screen top was removed. After making sure there is no mosquito left inside the cardboard container, it was carefully taken out and the net was tied closed. Behaviors of birds were then video recorded for one hour, after which birds were placed back to housing cages. After bird removal, cages were placed in a freezer for 15 min to kill mosquitoes. Numbers of fed and unfed mosquitoes were then recorded from each cage. Mosquito defense behaviors of birds were later scored for the first 15 min of the 1 h recording using JWatcher software. Scored behaviors included i) hops, ii) head movements, iii) pecks, iv) wing movements, v) foot movements, and vi) scratches. These behaviors were scored based on Gervasi et al. [40], and were predicted to affect mosquito-feeding success.

2.2.3. Female exposure

Our behavioral apparatus for this trial consisted of a main chamber (40w X 40d X 45 h cm) in which an untreated, novel, reproductively naïve but mature female finch was housed. The main chamber was connected to an arm (56w X 68d X 45 h cm) at the end of which a male zebra finch was placed in its own cage (56w X 56d X 45 h cm). The main chamber was separated from the arm with a plexiglass barrier (40wX45h cm). In the center of the main chamber, there was a perch (12wX23h cm), located 15 cm behind the plexiglass between the arm and the chamber. The rear end of the main chamber had food and water cups. An observation camera (Foscam, FI9821W) was mounted above the apparatus and connected to PC (Dell, Optiflex 7010) so behaviors of birds could be recorded. The observation room was lit with full-spectrum fluorescent bulbs with UV (Zoo Med, Repti Sun). For each behavioral trial, male birds were placed into the end of the arm in their individual cages. After 30 min of habituation, a female was introduced into the main chamber. During the subsequent 60 min, behaviors of males were recorded. Food and water remained in the males' cages. After 1 h of exposure to a female, males (8 Control, 6 Poly) were immediately sacrificed to collect brains for later analysis (see below). Behaviors of males were scored for 60 min using JWatcher software. Scored behaviors were i) hops on perches, ii) food cup visits, and iii) pecks at food.

2.3. Histology

2.3.1. Tissue preparation

Immediately after exposure to females, each male was deeply anesthetized with an intramuscular injection of Ketamine (50 mg/kg) and Xylazine (10 mg/kg), and then sacrificed by transcardial perfusion with a 0.9% phosphate buffered saline (PBS) followed by 4% paraformaldehyde in 0.1 M phosphate buffer (PFA) at pH 7.4. Brains were harvested, immersed in PFA for 24 h, then cryoprotected in 30% sucrose in PBS for 24 h. Brains were then frozen with dry ice, and left hemispheres were cut sagittally (40 μm-thick sections) using a microtome (Microm HM-400).

2.3.1.1. Brain volume analysis. One set of every fifth section was collected for brain volume analysis and for anatomical reference. Brain sections were mounted on slides with 40% gelatin mounting solution, and air-dried for a day. Slides were then stained with Cresyl Violet (Sigma Chemical, St. Louis, MO), dehydrated with series of alcohol baths (Ethyl-Alcohol 190 Proof, Pharmco-AAPER, Brookfield, CT), cleared with CirtriSolvTM (FisherbrandTM, Pittsburgh, PA), and finally cover-slipped with Permount (FisherbrandTM, Pittsburgh, PA) for storage.

2.3.1.2. Immediate early gene expression analysis. A set of brain sections adjacent to the ones used in volume analysis were collected for immunohistochemical analysis of IEG protein expression, specifically ZENK. Sections were first washed for ten minutes in PBS then incubated in 30% hydrogen peroxide (H_2O_2) in PBS for 15 min at room temperature. After washing 3× in PBS for 10 min each, sections were incubated in EGR- antibody solution (1:5000, SANTA CRUZ Biotechnology, C19, made in rabbit) buffered in 0.3% Triton-X/PBS overnight at 4 °C. The following day sections were washed initially 3× in PBS for 10 min each, before incubating them in secondary antibody (1:5000 biotinylated anti-rabbit IgG, VECTOR Labs, BA-1000) for 1 h at room temperature. After a secondary wash in PBS (3× for 10 min each), sections were incubated in avidin-biotin complex (avidin-biotin reagent + PBS + 0.3% Triton X-100 (NaCl) for 1 h for signal amplification (Vectastain Elite ABC kit, VECTOR Labs, PK-6100) at room temperature, and then washed 1× in PBS for 10 min each. Finally, the antibody labeled neurons were visualized by immersing them in diaminobenzidine (DAB) solution (0.025% 3,3′ diaminobenzidine + PBS solution) for 10 min and adding 8–12 drops of 3% H_2O_2 with an additional 10 min incubation. To stop reactions, sections were washed 3× in PBS 10 min each. Sections were mounted on slides with the mounting solution containing 40% gelatin and air dried for a day. Slides were then cleared with CirtriSolvTM (FisherbrandTM, Pittsburgh, PA), and finally cover-slipped with Permount (FisherbrandTM, Pittsburgh, PA) for storage.

2.3.2. Microscopy analysis

2.3.2.1. Brain volume analysis. Brain sections were examined under a macroscope (Wild M420 and Nikon SMZ 1500) and a microscope (Nikon Microphot FX). TnA and telencephalon were photographed with CCD/digital cameras (Spot Insight QE or Nikon DXM1200) mounted on either macro- or microscopes in 32× and 5× magnification(See Fig.3A,B). Volume measurements were based on a method described by MacDougall-Shackleton et al. [60]. Specifically, digital images were uploaded to graphics software (Canvas X, v16, Texas, 2014), and region boundaries were traced to compute areas. These areas were then multiplied by 200 μm and summed to produce the volume of the nuclei. To measure the telencephalon volume, sections used for TnA were photographed in a lower magnification to be able to capture whole TnA in one picture and volume was calculated multiplying measured areas by 200 μm to obtain the total volume.

2.3.2.2. Immediate early gene expression analysis. ZENK activity in TnA was analyzed based on a previous protocol [77]. Briefly, brain sections were examined under a macroscope (Wild M420 and Nikon SMZ 1500) and a microscope (Nikon Microphot FX) (See Fig. 3C,D). The lateral striatum (lSt) was selected as a control region of ZENK activity, as ZENK expression in this region is relatively stable in birds regardless of stimulus exposure [82]. For each animal, two sections were photographed with CCD/digital cameras (Spot Insight QE or Nikon DXM1200) mounted on either macro- or microscopes. For TnA, sections approximately 2.3 mm lateral to the midline were used. Sections for lSt were approximately 2.5 mm lateral to the midline. Digital images were uploaded to graphics software (NIH ImageJ, v1.51, Maryland, 2011) [90] in 8-bit gray-scale. Using the “Find Maxima” function, ZENK-immunoreactive cells were identified as localized spikes of chromatic value on an image. In a small section, before labeling, “Noise tolerance” was adjusted until every signal manually counted was correctly labeled (no extra or missing signals). Once this tolerance was adjusted, signals were automatically detected. In TnA, all positive signals were counted, and area of the TnA was recorded. In lSt, signals in a rectangle area

(0.2 × 0.3 mm) just dorsal to the globus pallidus were counted.

2.3.3. Statistical analysis

Statistical analyses were conducted with SPSS V24 (IBM Corp. Released 2016). To detect effects of Poly I:C challenge on birds' general activity, generalized linear mixed models (GLMM) were used. Treatment (Control or Poly), cohort, sex, treatment*cohort, treatment*sex, and trial number were fixed effects in the model, and bird id was used as a random effect. Repeated covariance type was First-Order Autoregressive, and a Poisson distribution with a log link was chosen based on visual inspection of behavioral variable distributions. Degrees of freedom were fixed for all tests. For fixed effects and coefficients, robust estimations were used to handle violations of model assumptions. Robust covariance matrices are suggested to be preferred over model-based covariance matrices if the main interest of the analysis is the fixed effects over random effects [54]. Finally, when appropriate, pair-wise comparisons were made using sequential Bonferroni corrections.

To detect effects of Poly I:C challenge on mosquito exposure responses and the number of mosquitoes that fed on the birds, generalized linear models (GLM) were used. Treatment (Control or Poly), cohort, sex, treatment*cohort, and treatment*sex were fixed effects and number of female mosquitoes was entered as a covariate in the model. A negative binomial error distribution was selected for distribution of behavioral variables, except gaping behavior, for which normal distribution with identity link was selected. The covariance matrix was robustly estimated, and the significance of fixed effects was investigated with Wald tests.

Behavior scores of males in the presence of a novel female violated assumptions of normal distribution. Hopping, food cup visits and pecking behaviors were positively skewed. Therefore, in order to detect effects of Poly I:C on behavior of males, Mann-Whitney *U* test was applied.

To detect effects of Poly I:C on TnA volume and ZENK activity, GLMs were fit. Treatment (Control or Poly) was the fixed effect, and telencephalon volume was the covariate in activity analysis. TnA volume distribution and the number of ZENK positive cells in the TnA were selected as linear. Covariance matrix was robustly estimated, and the significance of fixed effects was discerned with a Wald Chi-Square test. For the number of ZENK positive cells in the lSt, there was no covariate, as the measured volume was same for all birds. To detect an effect of Poly I:C on telencephalon volume, one-way ANOVA with treatment as a factor was used.

3. Results

3.1. General activities

Generalized linear mixed models of all three behaviors were statistically significant (Table S1). There was a significant interaction of sex and treatment on hopping behavior ($\beta = 0.712 \pm 0.287$, $t = 2.479$, $p = .014$); control females hopped more often than Poly females yet there was no effect of treatment on male hopping behavior (Fig. 1A). There was also a main effect of cohort on hopping behavior ($\beta = 0.441 \pm 0.126$, $t = 3.547$, $p = .001$), as first cohort birds hopped more often, and birds hopped more in the morning compared with the evening (Table 1).

In food cup visits, neither treatment nor sex had a significant effect (Table 1). However, there was again an interaction between treatment and sex ($\beta = 0.882 \pm 0.413$, $t = 2.136$, $p = .034$); control females visited the food cup more often than Poly females yet there was no treatment effect on males (Fig. 1B). Similar to hopping behavior, there was a main effect of cohort and time with the first cohort visiting the food cup more often ($\beta = 1.133 \pm 0.201$, $t = 5.460$, $p < .001$), and birds visited the food cup more frequently in the morning (Table 1).

Both sex and treatment revealed a significant main effect on the number of pecks at food (Table 1). Poly birds pecked at food less often than control birds ($\beta = -0.808 \pm 0.2$, $t = -4.308$, $p < .001$), and female birds pecked at food less often compared with males ($\beta = -0.549 \pm 0.180$, $t = -3.051$, $p = .003$). Again, however, there was a significant interaction between sex and treatment ($\beta = 0.508 \pm 0.220$, $t = 2.309$, $p = .022$), where Control females pecked at food more often than Poly females, but male treatments did not differ. Finally, birds pecked at food more often in the morning compared with evening records (Table 1), similar to hopping and visiting food cup behaviors.

3.2. Mosquito exposure

Behavior scores of three birds (two Controls and one Poly) were removed from the mosquito exposure analysis as their values for hopping were more than two standard deviations higher than mean responses and thus represented extreme outliers [71]. Overall, females hopped more than males when exposed to mosquitoes ($\beta = 2.205 \pm 0.963$, $\chi^2_{(1)} = 5.233$, $p = .022$), though we also observed a significant sex x treatment interaction whereby Poly I:C caused an increased response to mosquitoes in females but not males ($\beta = -2.105 \pm 1.033$, $\chi^2_{(1)} = 4.513$, $p = .042$) (Fig. 2A). In addition, Cohort 1 hopped more often compared with Cohort 2 ($\beta = 3.210 \pm 1.227$, $\chi^2_{(1)} = 6.845$, $p = .009$). However, there was not a significant interaction between treatment and cohort (Table 2). Finally, the number of female mosquitoes introduced to the cage negatively predicted hopping ($\beta = -0.162 \pm 0.038$, $\chi^2_{(1)} = 18.084$, $p < .001$); birds exposed to many mosquitoes hopped less than birds exposed to fewer (Fig. 2B). Omnibus tests for the models revealed that except hopping, behaviors of birds (including head movements, pecks, wing movements, foot movements, and scratches), were not different between treatment groups, sexes, and cohorts (Table S3 and Table S5 through Table S10).

Regarding number of bloodfed mosquitoes, treatment, sex, and cohort did not have a significant effect (Table S11). However, the number of female mosquitoes positively predicted the number of bloodfed mosquitoes at the end of mosquito exposure ($\beta = 0.136 \pm 0.031$, $\chi^2_{(1)} = 19.403$, $p < .001$) (Fig. 2C).

3.3. Brain Analysis

Telencephalon volumes did not differ between groups ($F(1,12) = 0.450$, $p = .515$) (Table S12), though Poly I:C treatment reduced the volume of the TnA compared to control birds ($\beta = 0.061 \pm 0.021$, $\chi^2_{(1)} = 8.419$, $p = .004$) (Fig. 4A). In addition, telencephalon volumes did not predict TnA volumes ($\beta = 0.011 \pm 0.009$, $\chi^2_{(1)} = 1.306$, $p = .253$) (Table 3).

Poly I:C treatment increased TnA activity (in response to exposure to a novel female) relative to controls ($\beta = -149.232 \pm 62.738$, $\chi^2_{(1)} = 5.629$, $p = .017$) (Fig. 4B). TnA volumes did not predict the number of ZENK positive neurons ($\beta = -160.698 \pm 433.020$, $\chi^2_{(1)} = 0.138$, $p = .711$) (Table 3). Moreover, lSt activity was not affected by Poly I:C treatment ($\beta = -6.208 \pm 22.961$, $\chi^2_{(1)} = 0.072$, $p = .787$) (Table 3). Finally, behaviors of Poly and control males did not differ in the presence of a novel female (Table S13).

4. Discussion

4.1. Effects of Poly I:C on behavior of adult birds

4.1.1. General activity

Poly I:C challenged female nestlings reduced their hopping, food cup visits, and pecking at food in adulthood relative to control females. Such effects were not observed in male zebra finches. Our results mirror other studies in birds showing effects of other ELICs on adult behavior [17,43]. These combined results indicate that an ELIC can induce

Table 1
Generalized linear mixed model of general activity behaviors of the birds.

						95% CI	
	Behavior	Coefficient	Std. error	t	Sig.	Lower	Upper
Intercept	*Hopping*	4.869	0.198	24.546	< **0.001**	4.478	5.260
	Food Cup	0.454	0.487	0.933	0.352	−0.506	1.415
	Pecking	4.245	0.324	13.121	< **0.001**	3.607	4.883
Treatment	*Hopping*	−0.355	0.240	−1.483	0.140	−0.828	0.117
	Food Cup	−0.066	0.346	−0.190	0.849	−0.748	0.617
	Pecking	−0.808	0.200	−4.308	< **0.001**	−1.203	−0.413
Cohort	*Hopping*	0.441	0.124	3.547	< **0.001**	0.196	0.687
	Food Cup	1.133	0.201	5.640	< **0.001**	0.737	1.529
	Pecking	0.204	0.184	1.108	0.269	−0.159	0.567
Sex	*Hopping*	−0.006	0.137	−0.045	0.964	−0.276	0.263
	Food Cup	0.170	0.216	0.789	0.431	−0.255	0.596
	Pecking	−0.549	0.180	−3.051	**0.003**	−0.904	−0.194
Treatment* Cohort	*Hopping*	0.097	0.289	0.334	0.739	−0.474	0.667
	Food Cup	−0.241	0.421	−0.0572	0.568	−1.072	0.590
	Pecking	0.345	0.224	1.541	0.125	−0.097	0.786
Treatment * Sex	*Hopping*	0.712	0.287	2.479	**0.014**	0.145	1.278
	Food Cup	0.883	0.413	2.136	**0.034**	0.068	1.699
	Pecking	0.508	0.220	2.309	**0.022**	0.074	0.942
Trial							
Morning 1	*Hopping*	0.515	0.184	2.792	< **0.001**	0.151	0.878
	Food Cup	1.752	0.479	3.658	< **0.001**	0.807	2.697
	Pecking	1.340	0.273	4.917	< **0.001**	0.803	1.878
Evening 1	*Hopping*	0.411	0.196	2.090	**0.038**	0.023	0.798
	Food Cup	−0.944	0.522	−1.808	0.072	−1.975	0.086
	Pecking	−1.087	0.384	−2.834	**0.005**	−1.844	−0.331
Morning 2	*Hopping*	0.407	0.131	3.098	**0.002**	0.148	0.665
	Food Cup	1.732	0.484	3.584	< **0.001**	0.778	2.686
	Pecking	1.464	0.260	5.683	< **0.001**	0.952	1.976
Evening 2	*Hopping*	0.251	0.164	1.526	0.129	−0.073	0.575
	Food Cup	−0.369	0.539	−0.684	0.495	−1.433	0.695
	Pecking	−0.371	0.279	−1.328	0.186	−0.922	0.180
Morning 3	*Hopping*	0.435	0.194	2.245	**0.026**	0.053	0.817
	Food Cup	1.698	0.532	3.195	**0.002**	0.650	2.747
	Pecking	1.457	0.283	5.138	< **0.001**	0.897	2.016

behavioral variation in adult birds, similar to patterns that have been observed following early-life exposure to other stressors [19,52,53].

In mammals, ELIC is well-known to affect activity level and feeding rate later in life, but the direction of the effects is not clear. Some studies showed decreased locomotor activity, and feeding rate [5,102], while other's reported opposite results [47,49,74,108]. Mammalian studies differ in various aspects, such as type of immune challenging agent (Poly I:C, lipopolysaccharide), behavioral apparatus (cylinder vs. open field), and age of animal during behavioral tests. For example, 180-day old prenatally infected rats reduced locomotor activity [102] whereas younger rats increased activity [47,108]. In the current study, we only observed behaviors of sexually mature zebra finches in the morning and evening, when the mosquito flight is at peak [103]. It is possible that the direction and effect of Poly I:C on general activity of birds may vary significantly in different ages of birds or in different tasks, similar to mammals.

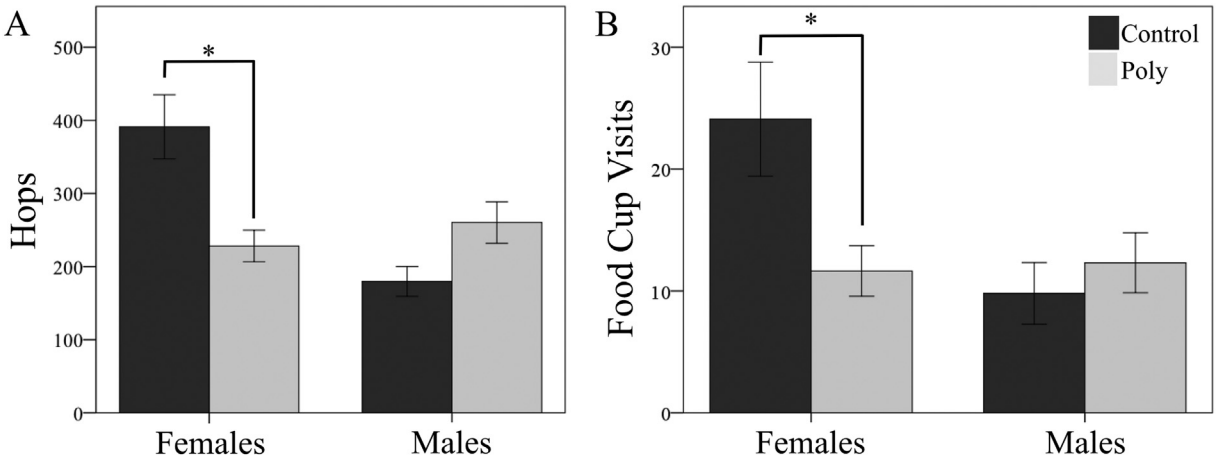

Fig. 1. Poly I:C challenge had sex-dependent effects on hopping and food cup visits of female but not male finches. Poly I:C challenged female finches (A) hopped and, (B) visited food cup less often in the morning and in the evening compared with control females. Male finches did not differ in their behavior. * indicates a significant difference of $p < .05$. Mean values and one standard error are shown.

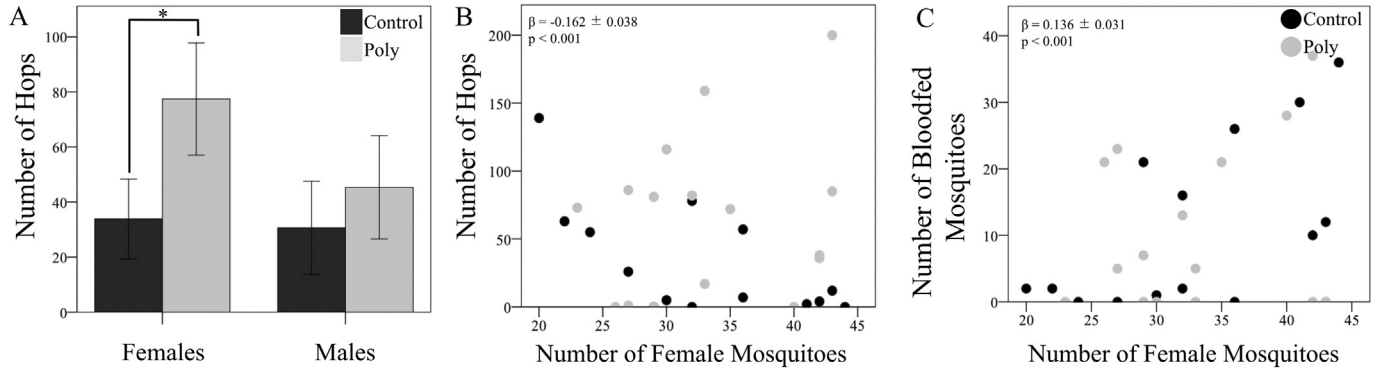

Fig. 2. Poly I:C challenge had sex-dependent effects on hopping behavior in the presence of mosquitoes. (A) Poly I:C challenged females hopped more compared with control females, but a similar effect was not observed in males. (B) Hopping behavior of birds depended on the number of female mosquitoes; as number of female mosquitoes increased, both control and Poly birds hopped less often. (C) Number of bloodfed mosquitoes was positively related with number of female mosquitoes. * indicates significant difference of $p < .05$. Mean values and one standard error are shown.

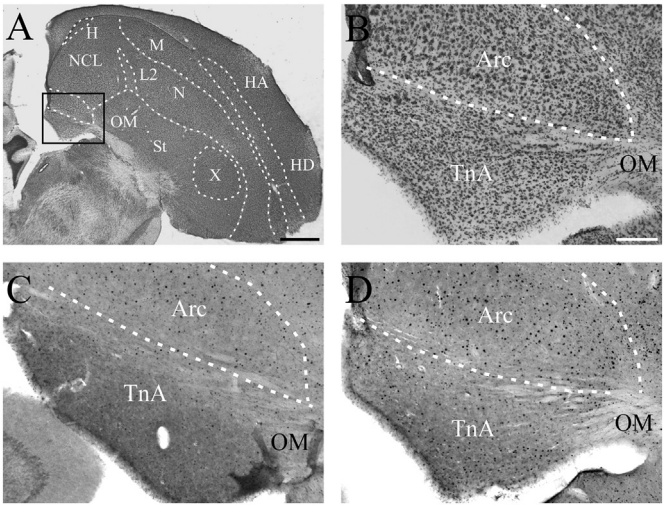

Fig. 3. Representative brain sections for Cresyl Violet stained (A, B) and immunohistochemically processed brain section (C, D). (A) Cresyl Violet stained brain section under 5× magnification for Telencephalon volume measurement, Scale bar: 1 mm. (B) Cresyl Violet stained brain section under 35× magnification for TnA volume measurement. Scale bar: 200 μm. (C,D) Immunologically stained sections under 35× magnification for ZENK-ir neurons in TnA of control (C) and of Poly (D) birds. TnA of control birds express fewer number of ZENK+ neurons compared with Poly birds. Dashed lines are the borders of different regions. Arc: Arcopallium, H: paraHVC, HA: Apical Hyperpallium, HD: Densocellular Hyperpallium, L2: Subfield of Field L, M: Mesopallium, N:Nidopallium, NCL: Caudolateral nidopallium, St: Striatum, TnA: Nucleus taeniae, OM: Occipitomesencephalic tract, X: Area X. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.1.2. Mosquito defense

We found that Poly I:C challenge increased hopping of females in the presence of mosquitoes compared with control birds (Fig. 2A). Darbro and Harrington [27] defined defensive behaviors as those behaviors that are rarely observed in the absence of parasites. In our study, except hopping, we did not find a difference in behaviors that were predicted to affect mosquito feeding success [40]. However, as hopping could occur in the absence of mosquitoes, which does not fall into definition of Darbro and Harrington [27] for defensive behavior, Poly I:C's effects on behavior might be broader than just defensive. Indeed, as above, Poly I:C affected activity in females in the absence of mosquitoes as well. Reactions to aversive stimuli, such as mosquitoes in the current study, are often observed via arousal and avoidance behaviors [33,111]. These results lead us to argue that Poly I:C might be affecting avoidance or arousal to an aversive stimulus more so than defensive behaviors.

In mammals, various studies have revealed effects of ELIC on behaviors relevant to avoidance of aversive stimuli. For example, in rats, adults prenatally exposed to Poly I:C emitted more aversive ultrasonic calls to a shock predicting tone [110]. Similarly, prenatal Poly I:C injections increased the latency of rats to leave dark compartments [62], and postnatal Poly I:C increased latency to enter open-field apparatuses [51]. Injecting rats with LPS yielded parallel results: postnatally-injected rats spent less time in the central zone of open field and light side of the light-dark box [55] compared with controls. A similar increase in avoidance behavior after an ELIC was also observed in mice [31,58]. Regarding arousal of animals after an ELIC, Sominsky et al. [93] showed that prenatal LPS injection caused higher respiratory rate after a mild stressor, indicating increased autonomic arousal in treated animals. Also, prenatal or postnatal LPS injection increased acoustic startle response of rats [38,39,105]. Although these studies are in mammals, they are consistent with our conclusion that Poly I:C as an ELIC

Table 2
Generalized linear model of hopping behavior in the presence of mosquitoes.

					95% CI	
	Coefficient	Std. error	χ^2	Sig.	Lower	Upper
Intercept	6.503	1.236	27.686	**< 0.001**	4.080	8.925
Treatment	0.824	1.168	0.489	0.480	−1.465	3.114
Cohort	3.210	1.227	6.845	**0.009**	0.805	5.615
Sex	2.205	0.963	5.233	**0.022**	0.316	4.094
Treatment*Cohort	−1.311	1.069	1.504	0.220	−3.406	0.784
Treatment *Sex	−2.105	1.033	4.153	**0.042**	−4.130	−0.080
Total Females	−0.162	0.038	18.084	**< 0.001**	−0.237	−0.087
Negative Binomial	1[a]					

a: Fixed at the displayed value. Coefficients that are redundant were omitted. Details are in Table S4.

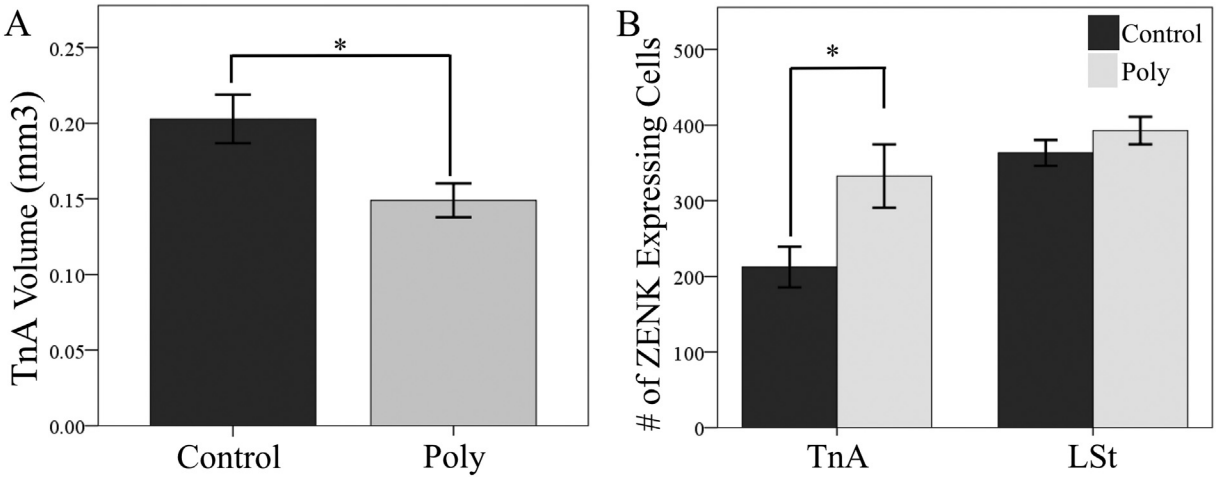

Fig. 4. Poly I:C challenge affected brain development and activity. (A) Poly I:C challenged males developed smaller TnA volumes. (B) Poly I:C challenged males had more ZENK+ positive cells in the TnA in the presence of a novel female. *: $p < .05$. Mean values and one standard error are shown.

increases avoidance behavior in zebra finches. Together with the results of decreased activity during the peak time of mosquito flight, such effects of Poly I:C on avoidance could be specific to certain stimuli that signal the possibility of disease transmission. Further studies are required to differentiate these effects from those in response to different adverse stimuli, such as predator cues or conspecific aggression.

In our study, we found no effect of Poly I:C challenge on mosquito feeding success, as mosquitoes equally bit both groups of birds. To our knowledge, ours is the first attempt to determine whether ELIC affects anti-vector behavior in adulthood. A few studies have investigated changes in behaviors of animals after an early life parasite exposure. In great tits (*Parus major*) and cliff swallows (*Hirundo pyrrhonota*), nestlings showed different rates of dispersal in adulthood depending on the level of flea parasitism during development [14,45]. Although these studies did not measure defenses directly, changes in the dispersal rate due to early nest parasite load were proposed to be adaptive [42]. The lack of an effect of Poly I:C challenge and mosquito foraging success in our study could also partly be due to the small size of the mosquito-proof cage. This cage allowed us to accurately observe active defenses such as pecks, or wing movements, but zebra finches would be comparatively unable to avoid mosquito attacks as they would under natural conditions.

4.2. Sex-dependent effects of Poly I:C and developmental stress

We found sex-dependent effects of Poly I:C on multiple traits; experimental females hopped, visited food cup, and pecked at food less than Control females. Poly I:C challenged females also differed in response to the presence of mosquitoes by hopping more often than control females. No such differences were seen in male birds. Previously, sex-dependent effects of ELIC were reported in zebra finches' learning abilities [43], although these effects were seen in males but not females. This discrepancy with our results could be due to three differences among studies. The first difference is the viral vs. bacterial nature of the treatment substance. In the current study, we used viral infection mimicking agent Poly I:C while Grindstaff et al. [43] applied LPS, an outer membrane component of bacteria. The second difference is the age at immune challenge. We injected nestlings with Poly I:C once on PD 14, while Grindstaff et al. [43] treated nestlings twice on both PD5 and PD28. Finally, the third difference is the behavioral measurements. We were interested in the general activity and mosquito defense behaviors of nestlings while Grindstaff et al. [43] compared learning abilities of nestlings for a novel foraging test. All these differences warrant follow-up studies to examine in detail whether different immune challenging agents affect male and female birds

Table 3
Generalized linear models of TnA Volume, TnA Activity, and lSt Activity.

						95% CI	
		Coefficient	Std. error	χ^2	Sig.	Lower	Upper
TnA Volume	Intercept	0.051	0.103	0.244	0.621	−0.151	0.253
	Treatment						
	Control	0.061	0.021	8.419	**0.004**	0.020	0.102
	Poly	0[a]					
	Telencephalon	0.004	0.005	0.729	0.393	−0.006	0.014
	Scale	0.002[b]	0.001			0.001	0.004
TnA Activity	Intercept	417.244	75.3824	30.637	< **0.001**	269.498	564.991
	Treatment						
	Control	−149.232	62.738	5.658	**0.017**	−272.197	−26.267
	Poly	0[a]					
	TnA Volume	−160.698	433.020	0.138	0.711	−1009.403	688.006
	Scale	6714.284[b]	3002.719			2794.672	16,131.2
lSt activity	Intercept	364.333	17.806	418.685	< **0.001**	329.435	399.232
	Treatment						
	Control	−6.208	22.961	0.073	0.787	−51.211	38.794
	Poly	0[a]					
	Scale	1776.015[b]	671.271			846.687	3725.38

a: This coefficient is set to zero because it is redundant. b: Maximum likelihood estimate.

separately.

Other stressors in early development, are known to also cause sex-dependent effects in birds. For example, zebra finch males raised in smaller broods were more attractive than males from larger broods, but size of the brood did not affect female attractiveness [30]. Corticosterone (CORT) exposure during development also reduced neophobia in males with no effect on females [95]. Another study showed that a CORT exposure increased risk assessing behaviors, such as head turns in a novel environment, but only in females [35]. While studies described above were all based on zebra finches, similar sex-dependent findings of early life stressor exposure have also been reported in chickens [41] and song sparrows (*Melospiza melodia*) (Sc[87,88]). A comparison of effects of stressors and ELIC suggest that both sexes are susceptible to adverse early life environments, though depending on the task or measurement of interest effects could be observed as sex-dependent. For example, in the current study, Poly I:C injected females showed more avoidance behaviors, and Emmerson and Spencer [35] showed increased risk assessing behaviors in CORT exposed females compared to control females. In males, CORT exposure reduced neophobia [95]. It is possible that adverse early life conditions program females to be risk-avoidant, and males to be risk-seeking. Future ELIC studies should test this possibility by comparing risk-taking behaviors of birds in different settings such as measuring latency to approach feeders that startle birds (Martins et al., 2007).

Supporting the conclusion that sex-dependent effects depend on the task, other early life stress studies showed both males and females were affected. For instance, low-quality diets (with respect to the protein content) caused both male and female zebra finches to have smaller adult mass [12]. Also, compensatory growth rate due to low-quality diet caused a high resting metabolic rate [24], affected colour association with food [15,37], and increased latency to approach to a novel object [53] in both males and females. Although artificial CORT exposure had sex-dependent effects in some studies described above [35,41,87,88,95], it also has similar effects on males and females. For instance, CORT treatments in early-life affected social behaviors (foraging with parents) equally in both sexes [13], and social learning switched from vertical to oblique transmission [36]. If observing sex-dependent effects depend on the task as discussed above, future Poly I:C or ELIC studies should observe social behavior as in CORT exposure to test this conclusion.

In mammals, and rodents in particular, ELIC using Poly I:C caused both sex-dependent and independent effects [68]. For example, Poly I:C injection to pregnant mice impaired prepulse inhibition [56], working memory [21], and novel object recognition [76] of both male and female offspring. However, other studies find sex-dependent effects of Poly I:C [4,9,47,79,113]. For instance, Poly I:C injection to pregnant rats decreased startle response amplitude in females [104], and decreased the response rate of males [65]. One explanation for such variable responses to Poly I:C in rodents could simply be species/strain differences. Most sex independent results occurred in mice [21,56,69,70,76,81,91], but see [9], whereas sex-dependent results were found in rats [4,47,65,79,113], but see [85,102]. The current study is the first to our knowledge that investigated ELIC using Poly I:C as an agent in birds. The difference in results on sex dependency in rodents between rats and mice as above warrants further studies with other song birds to determine if Poly I:C has sex dependent effects in other species as well similar to rodents.

Another possible explanation of sex-dependent effects of Poly I:C challenge could involve the dimorphic immune system of finches and animals broadly. Female birds have a stronger immune system as longevity is more important for females than males [63,86]. An ELIC, such as the one used in this study, could cause competition for limited resources, such as nutrients, due to strong immune response in the developing body of the female nestlings. This investment in immune system could have programmed female behaviors differently than males. Because we used a single Poly I:C injection in this study, it is possible that changes in adult behavior represent long-term programming for future environment [32]. In this light, Poly I:C challenged females might have invested more in immune defense while trading off performance in other (e.g., reproductive) systems [29].

4.3. Effects of Poly I:C on TnA of male zebra finches

4.3.1. Effect of Poly I:C on TnA volume

Several previous studies found that early-life stressors can affect avian brain development [46,59,94]. However, to our knowledge, ours is the first to consider effects of a viral immune challenge on brain development. We found that Poly I:C challenged males developed smaller TnAs than controls.

The majority of the previous avian studies on developmental stressors in birds have focused on effects on song nuclei. Some studies reported effects of developmental stressors on song-related structures, such as either HVC (a letter based name) [16] and/or robust nuclei of arcopallium (RA) ([75,89]. In mammals, Poly I:C injection to pregnant rats also reduced amygdala volume [25] and altered the cytoarchitecture of amygdala in offspring [78].

In the current study, we did not find a difference in the behaviors of males in the presence of a novel female due to smaller TnA volume as seen in mammals with smaller MeA [22]. It is possible that behavioral changes require a much bigger effect on TnA. It is also possible that our experimental design failed to catch the effects of Poly I:C on sexual behaviors of males. To isolate the sexual arousal of males from courtship behaviors such as mounting, we tested males in a different cage. Placing males and females into a same cage could have revealed Poly I:C's effects on male sexual behaviors. Further studies of TnA and ELIC with different designs would inform us on how abnormal development of brain regions involved in socio-sexual behaviors would affect the success of males in reproduction. Comparing effects of an ELIC on TnA and MeA would also inform us more on the proposed homologies of those brain regions between mammals and birds.

4.3.2. Effect of Poly I:C on TnA activity

The TnAs of Poly I:C challenged males were more active than Control birds. Again, our study is the first to study IEG activity in the medial amygdala or the TnA after an ELIC in birds or mammals. Prenatal Poly I:C injection increased glucose metabolism in amygdala of adult rats [44]. Although not an ELIC, a postnatal stressor increased Fos immunoreactivity in the medial amygdala of rats [101], although a similar study did not find such a difference [100]. There are small differences between protocols of developmental stress between those two studies (removing litter vs. removing the dam, 16 vs. 20 days of separation), but as a medial amygdala homologue, results of mammalian studies support that physiology of TnA was affected by Poly I:C challenge.

TnA plays a role in the sexual behavior of birds [18,48,98]. For example, male quail that copulate with a female exhibit higher numbers of egr-1 positive cells compared with control males that did not copulate [18]. Also, if the quail was naïve to the female exposure, *c-fos* expression in TnA was higher in naïve birds compared with males experienced a conditioned stimulus that predicted visual female stimulus with no copulation chance [98]. In the current study, male zebra finches were only physically isolated while visually and acoustically exposed to female stimuli in their housing room. Therefore it is possible that in our experimental setup, repeated exposure to female birds with no possibility of copulation might have inhibited TnA activity similar to Taziaux et al. [98] study. Poly I:C exposure during development, on the other hand, might have impaired this inhibition and resulted in higher number of ZENK positive cells in TnA of Poly birds.

Another possibility for higher TnA activity in Poly I:C could be increased basal activity of the region. As above, Poly I:C challenge caused increased glucose metabolism in rats [44]. Also, offspring of malnutritioned dams showed increased baseline expression of egr-1

positive cells in their amygdala [73]. It is possible that simple exposure to a female bird did not affect TnA activity. Instead, the difference between groups could be due to increased basal activity caused by Poly I:C challenge early in the life.

The third possibility is the morphological changes in TnA. ZENK expression in TnA could have increased because of changes in the neuronal density of the entire TnA, rather than an increase of ZENK-expressing neurons as the Poly males had smaller TnA compared with control males. In that case, it would suggest that overall ZENK activity in TnA was similar between groups. It is also possible that the neuron number was fewer in Poly I:C challenged males due to pathological effects of Poly I:C on neurons. TnA could become hyperactive to compensate for the loss of neurons. This hyperactivity may be similar to an increase in activity found in neurological diseases such as Parkinson's disease [80,114]. However, since neuron number was not counted in the current study, further research is required for detecting possible physiological changes in TnA.

5. Conclusion

Our study is the first to examine the long-term effects of an early life viral infection on behavior and brain of adult birds. Results supported the hypothesis of long-term effects of an ELIC on animals. Poly I:C injection early in the life had sex-dependent effects, as only female behavior was affected by Poly I:C exposure. Females challenged early in life may show more avoidance behavior as discussed above and may change their behaviors to decrease the possibility of mosquito-borne infections in adulthood (i.e., less activity in the morning and the dawn, more activity in the presence of mosquitoes). This decreased infection rate would eventually increase the fitness of the female and change disease transmission rates in a population. In males, our study did not find a behavioral difference between treatments. However, it is possible that with different behavioral tests and measurement, Poly I: C's effects on males could also be revealed. On the other hand, Poly I:C injection affected brain development and activity in the TnA. Although those changes did not affect behavior of the males in the presence of females in the current study, further research is required to look in detail to courtship behaviors of males such as directed song to females.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.physbeh.2018.08.004.

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