Adolescent neural processing differences in orbitofrontal cortex[1], nucleus accumbens, and dorsal striatum during motivated behavior

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1. Introduction

Adolescence is a time of adjustment as one completes the physical and psychosocial transitions to adulthood. It is also considered a period of vulnerability as it coincides with the onset of symptoms for several major psychiatric problems, including mood disorders, schizophrenia, and drug abuse[2-3]. In recent years, studies in adolescent humans and animal models have described age-related shifts in cellular and molecular brain architecture and disparities in the pharmacological effects of various drugs[4]. Differences in measures of adolescent functional neural activity and connectivity have also been described, however, little is known of the precise nature of these age-related changes at the neuronal level.

We recorded single-unit activity from the orbitofrontal cortex (OFC), nucleus accumbens (NAc) and dorsal striatum (DS) of adolescent and adult rats as they performed a reward-motivated task. Neural activity was examined in the context of similar behavior (i.e. a "behavioral clamp") to determine whether adolescents processed the same salient events in a fundamentally different way from adults. Such findings could indicate age-related differences in neural processing efficiency, the encoding of salient events, and/or the impact of such events. By using techniques like single-unit electrophysiological recording in behaving laboratory animals, we can more precisely identify age-related processing differences, and develop and test hypotheses that relate them directly to both the increased risky behavior of normal adolescence and the onset of psychiatric problems that often arise at this time.

3. Electrophysiology Results

Figure 3. Adolescent OFC units were less inhibited & more activated

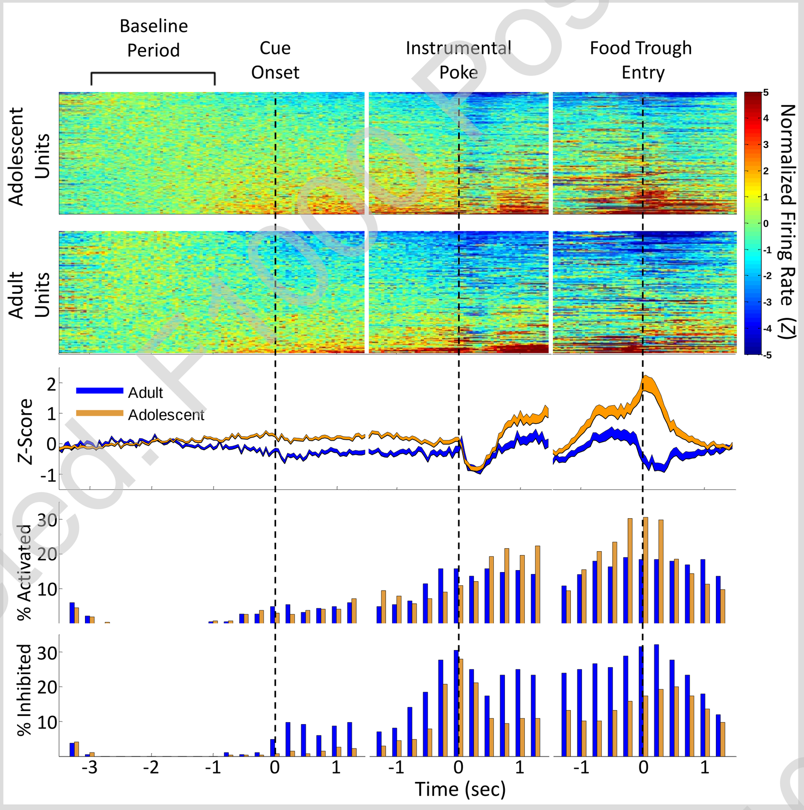


Figure 4. Heat plots represent the baseline-normalized firing rate for each adolescent (8 rats, 265 units; upper plots) and adult (4 rats, 184 units; lower plots) OFC unit during sessions 3-6. Each row is an individual unit's *Z*-score normalized firing-rate activity aligned to events of interest. Below the heat plots, average normalized population activity +1 *SEM* are presented. Activity is lower for adults than adolescents during several salient task events, especially during reward (food trough entry). The percentage of activated and inhibited units around task events reflect the adult tendency for more inhibition (generally) and less activation during reward.

Figure 5. Adolescent and adult NAc units showed similar patterns of activity

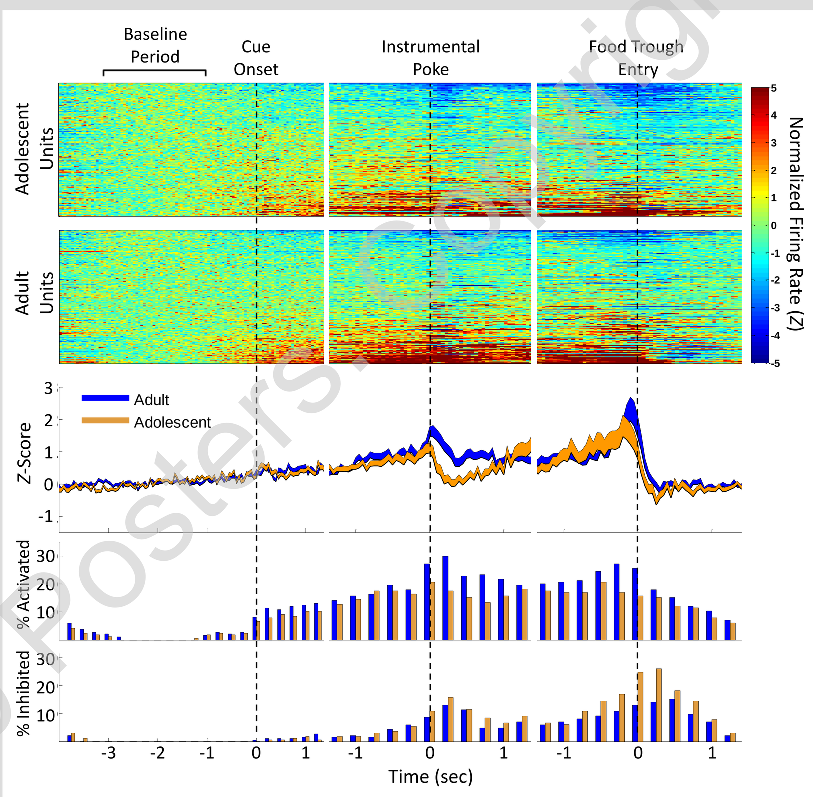


Figure 6. Following the same conventions as figure 4, the neural activity of all adolescent (10 rats, 165 units) and adult (8 rats, 184 units) NAc units are shown for sessions 4-6. The onset of each trial was associated with the similar activation of particular units that remained activated until entry into the food trough. Adults activated larger proportions of units at the instrumental poke and food trough entry, while adolescents inhibited a larger proportion of units at food trough entry. However, these differences were modest and transient, as the general time course and proportions of activated and inhibited units were often quite similar between groups in NAc.

Figure 6. Only adolescent DS units exhibited reward-anticipation

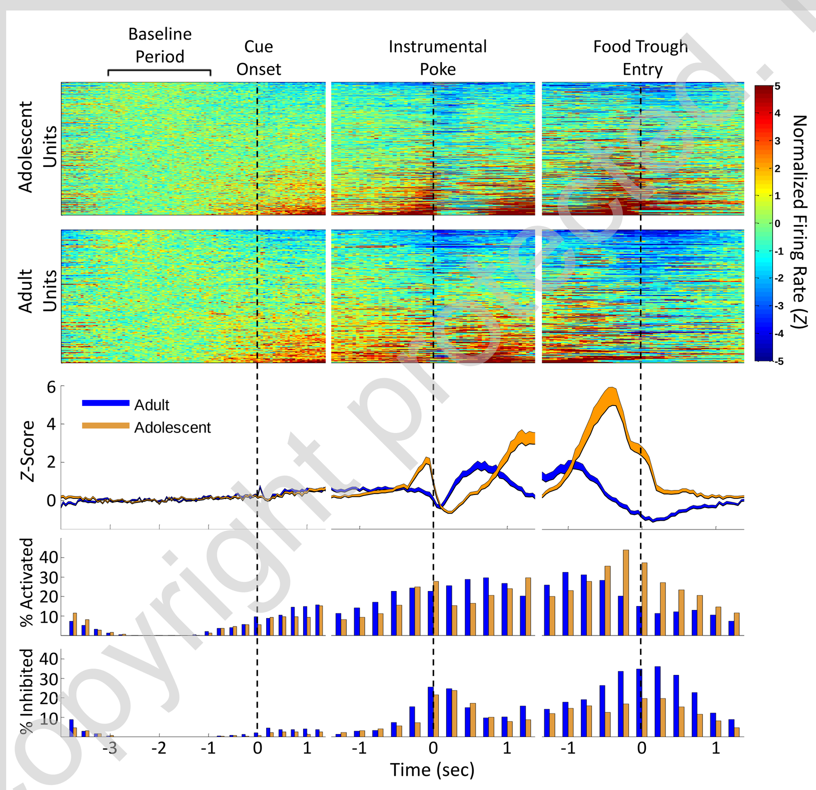
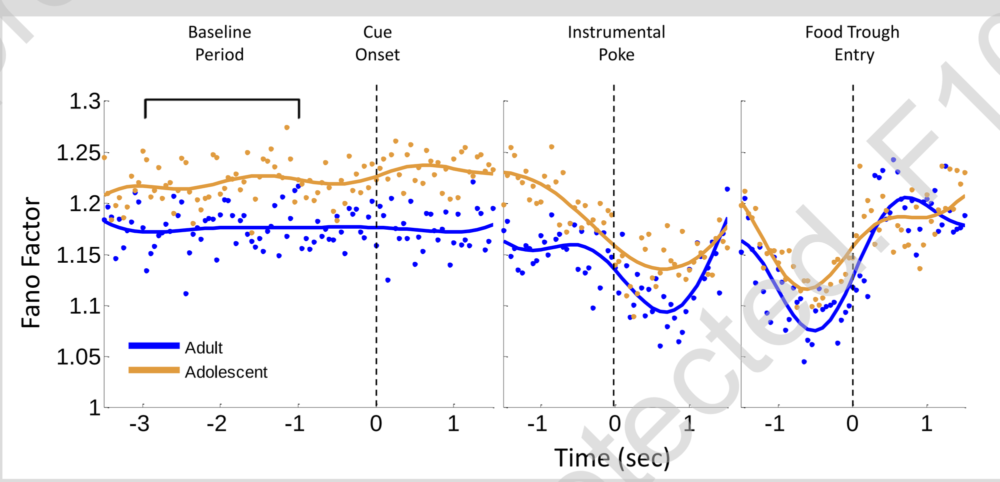


Figure 7. Striking age-related differences were found when comparing the activity of adolescent (10 rats, 322 units) and adult (8 rats, 248 units) DS units during sessions 4-6. Both groups contained neurons that activated prior to the instrumental poke, became inhibited, and then again activated before rats entered the food trough. For adolescent units, the interim period of inhibition was far longer, with activation persisting all the way through reward retrieval. In addition to peaking later, adolescent units were more strongly activated, and adult units were more inhibited around the time of reward. This pattern was reflected in unit category proportions as well.

Figure 4. Greater adolescent OFC variability

Figure 5. The Fano factors (trial-by-trial spike-count variance divided by spike-count mean) are shown for adolescent and adult OFC units during sessions 3-6, along with fitted polynomial lines. Adolescents tended to have higher Fano factors than adults, except after food trough entry. These data reflect Fano factor calculations performed with a mean-matching algorithm that held firing-rate distributions approximately constant[6].



This allowed the Fano factor time course to reflect changes in variance only. These data were very similar to raw Fano factor calculations (not shown). Thus, adolescent neurons exhibited more trial-by-trial variability than that of adults.

Table 1. Unit activity in selected windows

	Orbitofrontal Cortex		Nucleus Accumbens		Dorsal Striatum	
	Activated	Inhibited	Activated	Inhibited	Activated	Inhibited
Cue (0 to 0.5 s)	Adult: 6 (3.3%) Adol: 10 (3.8%)	Adult: 17 (6.4%) Adol: 2 (1.1%)	Adult: 21 (11.4%) Adol: 13 (7.9%)	Adult: 2 (1.1%) Adol: 1 (0.6%)	Adult: 22 (8.9%) Adol: 30 (9.3%)	Adult: 11 (4.4%) Adol: 7 (2.2%)
Poke (-0.5 to 0 s)	Adult: 21 (11.4%) Adol: 19 (7.2%)	Adult: 34 (18.5%) Adol: 21 (7.9%)	Adult: 33 (17.9%) Adol: 27 (16.4%)	Adult: 11 (6.0%) Adol: 9 (5.5%)	Adult: 60 (24.1%) Adol: 80 (24.8%)	Adult: 38 (15.3%) Adol: 23 (7.1%)
Poke (0 to 0.5 s)	Adult: 25 (13.6%) Adol: 32 (12.1%)	Adult: 46 (25.0%) Adol: 56 (21.1%)	Adult: 55 (28.8%) Adol: 29 (17.5%)	Adult: 24 (12.6%) Adol: 26 (15.7%)	Adult: 63 (24.8%) Adol: 49 (15.1%)	Adult: 61 (24.0%) Adol: 76 (23.5%)
FT Entry (-0.5 to 0 s)	Adult: 35 (19.0%) Adol: 80 (30.2%)	Adult: 53 (28.8%) Adol: 42 (15.9%)	Adult: 50 (27.2%) Adol: 28 (17.0%)	Adult: 20 (10.9%) Adol: 28 (17.0%)	Adult: 50 (19.9%) Adol: 141 (43.1%)	Adult: 83 (33.1%) Adol: 54 (16.5%)
FT Entry (0 to 0.5 s)	Adult: 34 (18.5%) Adol: 79 (29.8%)	Adult: 59 (32.1%) Adol: 51 (19.3%)	Adult: 33 (17.8%) Adol: 25 (15.2%)	Adult: 26 (14.1%) Adol: 43 (26.1%)	Adult: 28 (11.2%) Adol: 87 (26.7%)	Adult: 89 (35.6%) Adol: 63 (19.3%)

Table 1. Windows of interest were time-locked to the cue, instrumental poke (Poke) or entry into the food trough (FT). The number of adolescent (Adol) and adult units (and percentage) that were activated or inhibited are shown. Significant ($p < 0.05$) age-related proportional difference are indicated with red type.

2. Methods & Behav Results

Subjects & Surgeries

Adolescent (P28; n = 24*) and* adult (older than P70; n = 16) male Sprague-Dawley rats were implanted in OFC, NAc, or DS with 8-wire microelectrode arrays while under isofluorane anesthesia. In one cohort, recordings were made from the OFC alone, while another had implants bilaterally in DS and/or NAc. Rats recovered from surgery for approximately one week prior to behavioral testing. Protocols were approved by the University of Pittsburgh Animal Care and Use Committee.

Behavioral Task

Rats learned to poke into an illuminated center nose-poke hole for food pellet reinforcement in a standard operant box apparatus (Figure 1)[5].

Electrophysiology

All recordings were done while rats performed the behavioral task. Electrodes were connected to lightweight cabling attached to a commutator that allowed animals to move in an unrestricted fashion during recording. Behavioral event markers from the operant box were sent to neural recording software to mark events of interest. Single units were isolated offline using a combination of manual and semi-automatic sorting techniques.

Figure 1. Task overview

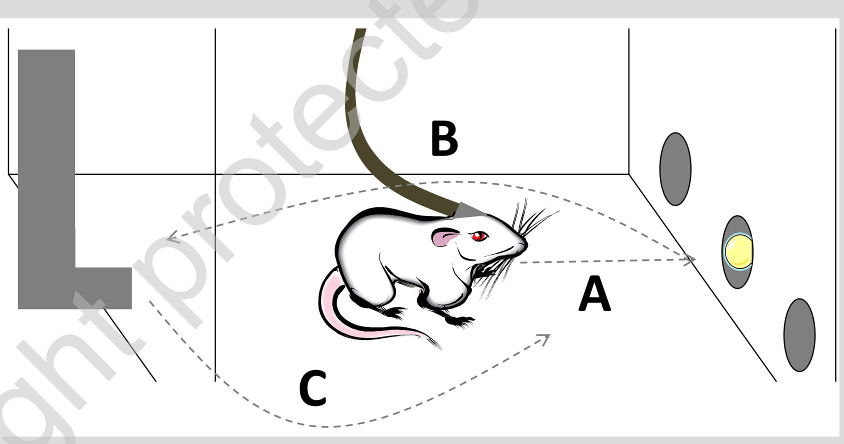


Figure 1. After the onset of the cue light in the center hole, the rat pokes into that hole (A). Doing this leads to the immediate delivery of a sugar pellet. The rat then approaches the food trough (B) to retrieve that pellet. After poking in the food trough a 5 sec inter-trial interval (C) is triggered before the next trial begins. Each session terminates after 100 trials or the passage of 30 min.

Analysis

Peri-event time firing-rate histograms were produced for each unit in windows around task events. The cross-trial average firing rate of each unit was *Z*-score normalized to that of its baseline period. Units were categorized as "activated" or "inhibited" within windows of interest based on whether their average normalized activity contained three consecutive 50 ms bins with $Z \geq 2$ or $Z \leq -2$, respectively. Comparisons of proportions of activated and inhibited neurons were done using χ^2 analyses and post-hoc *Z*-tests for two proportions. Analyses of cross-trial spike count variability were calculated as Fano factors (spike count variance/mean) using 80 ms moving windows in 50 ms steps. A mean-matching algorithm was used to confirm that the Fano factor results primarily reflected variance rather than changes in mean firing rate[6].

Figure 2. Similar behavior

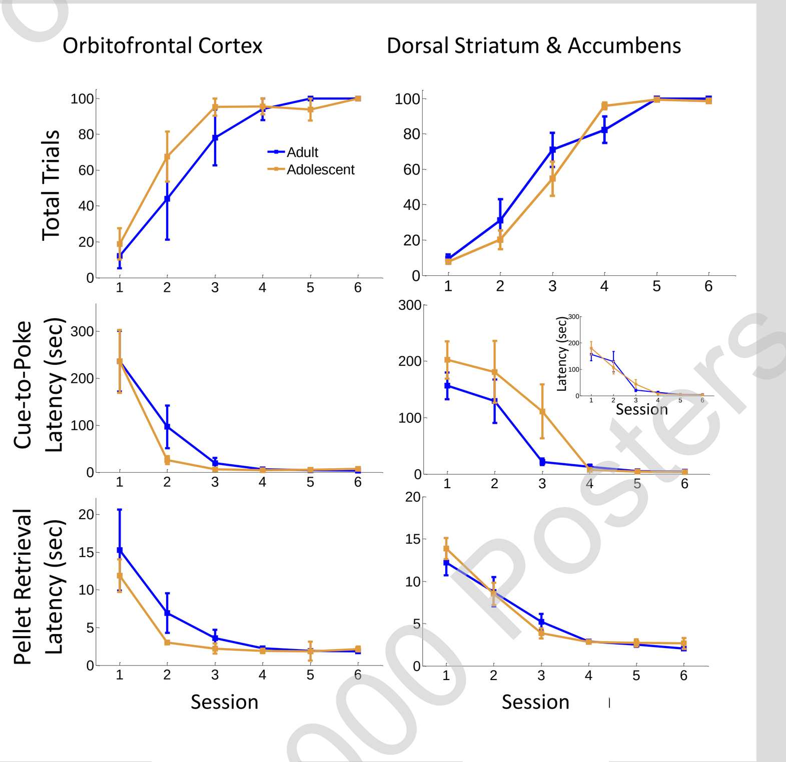


Figure 2. There were no significant behavioral differences between adolescents and adults in either cohort. Performance was maximal in OFC animals by session 3 and DS and NAc animals by session 4.

4. Summary

Orbitofrontal Cortex

- Adolescents exhibit less inhibited activity through much of the task except during the instrumental poke (at which time neural activity was indistinguishable for the two age groups).
- Adolescent units were more activated (in proportion and extent) to reward, with activity peaking somewhat later than that of adults.
- Adolescent neural activity was more variable from trial to trial, perhaps indicating that the timing of spiking activity was less tightly controlled in these younger animals.

Nucleus Accumbens

- A portion of units in both groups became activated with the onset of each trial. These units remained activated until reward retrieval.
- Adolescents had a smaller proportion of activated units at the instrumental poke and reward retrieval; they had a larger proportion of inhibited units at reward retrieval.
- Despite these transient differences, the general patterns of activity were quite similar for the two age groups, as reflected in the average normalized population activity.

Dorsal Striatum

- While trials began similarly, with the activation of a small proportion of units to the cue, several persistent age-related differences were observed.
- Both adolescents and adults contained neurons that became activated, inhibited, and then activated again. The time-course of this pattern was quite different, however.
- Adolescent units maintained activation until entry into the food trough, indicating a correlate of reward- anticipation or approach in these younger animals only.

5. Conclusion

Even as adolescents similarly performed the same motivated behavior as adults, their neural encoding of salient events, especially reward, fundamentally differed in the orbitofrontal cortex and dorsal striatum. Adolescent nucleus accumbens activity was far more similar to that of adults, indicating that the trajectory of functional neurodevelopment is highly region-specific.

References

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Acknowledgements

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