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Research report

Single unit activity during a Go/NoGo task in the ''prefrontal cortex'' of pigeons

T. Kalt *, B. Diekamp, O. Güntürkün

AE Biopsychologie, Fakultät für Psychologie, Ruhr-Universität Bochum, GAFO 05 / 618, 44780 Bochum, Germany

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Abstract

Single unit activity was recorded during a delayed auditory/visual Go/NoGo task from the neostriatum caudolaterale (NCL) of pigeons, a multimodal associative avian forebrain structure comparable to the prefrontal cortex (PFC). The animals were trained to mandibulate (to open their beak) during the Go period after which they received a drop of water as reward. Neuronal activity changes were observed during the delay period (DELAY) between auditory and visual stimulation, to the onset of the visual stimulus or to the delivery of the reward. In some neurons, responses were related to the behavioral significance of the stimulus such that the neuronal activity was statistically different between Go and NoGo trials. Moreover, some units anticipated the upcoming reward or changed their firing frequency in a correlated manner prior to beak movements. These neuronal activity patterns suggest that the NCL provides a neural network that participates in the integration and processing of external stimuli in order to generate goal directed behavior.

Keywords: Delay; Reward; Bird; Forebrain; NCL

1. Introduction

The neostriatum caudolaterale (NCL), a semilunar region in the caudalmost subventricular part of the avian forebrain is a multimodal association area that receives afferents from all major secondary sensory areas within the pigeon brain [27,28,41]. Moreover, the ventral tegmental area (VTA) feeds a dense dopaminergic innervation to the NCL whose definition and exact delineation is based on this mesencephalic input [7,8,54]. There is a massive projection from the NCL to the archistriatum [27] which is thought to be partly equivalent to mammalian sensorimotor cortex and whose more posterior parts are implied in viscerolimbic functions [30].

Based on similarities in the connectivity pattern and the behavioral consequences of lesions the avian NCL is suggested to be equivalent to the mammalian prefrontal cortex (PFC). [3,6–9,54,60]. PFC as well as NCL both receive dense dopaminergic afferents as well as projections from secondary auditory, visual and somatosensory areas of the telencephalon and are hence multimodal association structures [28,32,37,42]. Efferents of both areas innervate the basal ganglia as well the motor and premotor cortex in mammals and the archistriatum in birds [18,26,42,52]. The PFC participates in the planning and execution of movements especially when mediating cross-temporal contingencies [13]. One key aspect of this function is the ability of the PFC to mediate working memory by temporary holding goal-relevant sensory stimuli [18,33]. By this means, behaviorally relevant information can be used to generate goal-directed behavior even if it is no longer present at the time of response generation. In accordance with this function lesions of the NCL lead to cognitive deficits in tasks like delayed alternation which test working memory function [14,15,20,34,35] and experiments like reversal learning which assess rapid behavioral flexibility [22]. At least, larger NCL-lesions also interfere with Go/NoGo performance which tests the ability of the animal to sequence its behavioral pattern [20,22]. None of these cognitive deficits are accompanied by an attenuation of sensory discrimination accuracy [22,34,35]. Thus, it is concluded that the PFC and the NCL are multimodal association areas that subserve information processing in

Abbreviations: DELAY, delay period; DA, dopamine; NCL, neostriatum caudolaterale; PFC, prefrontal cortex; REWARD, reward period; STIM, stimulus period; STIM-ON, first 200 ms of the stimulus period

* Corresponding author. Fax: +49-234-709-4377; E-mail: thomas.kalt@ruhr-uni-bochum.de

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cognitive tasks and whose short-term and motor-set functions seem to lay the bridge from perception to action [13].

This is compatible to the conjecture that the NCL is involved in the integration of external sensory and internal homeostatic information for the purpose of generating motor plans. In this scheme, higher order sensory information is processed inside the NCL and conveyed to premotor and motor structures like the archistriatum and the basal ganglia in order to generate an appropriate behavioral response. If the similarities to the PFC hold, the consequences of executed behaviors might be fed back to the NCL via the dopaminergic VTA projection, since mesencephalic dopamine (DA) is known to mediate reward mechanisms [47]. This accords with the results of Durstewitz et al. [9] which demonstrated the NCL to be characterized by a high number of neurons which are presumably D_1-receptor positive and which receive a dense dopaminergic innervation via 'basket'-type synapses. Thus, NCL might constitute a neural matrix which is constantly modified according to the consequences of the animals' behavior and which is critically involved in planning behavioral outputs.

If this hypothesis holds, at least some neurons of the NCL should:

1. respond to the relevant sensory stimuli accompanying a learned task, if reward delivery is contingent with this stimulus,
2. code for certain aspects of the appropriate behavior,
3. have the property of 'memory cells' in being active during delay periods (DELAY) in which relevant sensory information has to be held for responses at a later time.

This study aims at testing these predictions by means of an electrophysiological characterization of NCL neurons in a behavioral task that affords the sequential organization of behavior over time in order to achieve a certain goal. Some of these findings have been published in abstract form [24].

2. Materials and methods

2.1. Subjects

Five pigeons (*Columba livia*) were trained to perform an auditory/visual Go/NoGo task. Three of these were utilized for repeated extracellular recordings, the remaining animals served as a control group to test working memory performance (see Section 2.3 for details). One animal was subjected to electrophysiological recordings and behavioral working memory testing. The individuals were prepared for recording by implanting a head-fixation block and a recording chamber under anesthesia with a mixture of ketamine hydrochloride and xylazine (40 mg/kg and 8 mg/kg i.m., respectively). The recording chamber was fixed to the posterior-lateral skull with dental acrylic at a location directly above the NCL according to coordinates obtained from the Karten and Hodos [25] stereotaxic atlas of the pigeon brain. After a recovery period of 7 days, the animals were put on a water deprivation schedule. Consumption of water was restricted to the daily training and recording sessions, i.e., animals were deprived of water for 24–36 h before each session. Additionally, animals had free access to water in their home cage for 20 min after each session. Food was available ad libitum in their home cage.

2.2. Apparatus

During training and recording sessions, the pigeon was restrained by a loose cloth bag and placed on a foam couch in front of a translucent screen (25 cm high and 30 cm wide). Its head was fixed into stereotaxic coordinates by the headholder (Fig. 1A). Mandibulation, i.e., opening of the beak, was monitored using an infra-red light emitting diode (BPW 23) and a photodetector (BPW 40) that were positioned to the side of the beak. The output from the photodetector was converted into TTL pulses and fed into a computer controlling the behavioral experiment. As a positive reinforcement, water was presented in a small aluminum container ($1 \times 1 \times 2$ cm^3) that was adjusted into position such that the tip of the beak was 3 mm below the water surface. The amount of water in the container was controlled by the computer through two electromagnetic valves (Kuhnke 65111). The influx and efflux valves were timed such that about 0.15 ml of water were available for about 3 s during which the pigeon was allowed to drink.

2.3. Behavioral task

The pigeons were trained in a combined auditory/visual Go/NoGo discrimination task (Fig. 1B). Following a 14–16 s randomly varying intertrial interval, single or double click sounds were presented and after 0.7 s delay a corresponding red or green light stimulus appeared on the screen for 3 s. Auditory and visual stimulation was redundant such that the appearance of a double click predicted successive stimulation with red light whereas a single click was always followed by presentation of green light. Only mandibulations during the stimulus period (STIM) were considered a behavioral response whereas mandibulations outside this period, e.g., delay or intertrial period had no consequences at all. Opening of the beak triggered the start of the reward or punishment period as well as the immediate termination of the visual stimulation. If red light was presented a behavioral response during the 3 s STIM period was rewarded with access to water for 3 s. Additionally, the availability of water was indicated by a white light mounted underneath the water receptacle. Failure to respond to the Go stimulus did not lead to a correction trial or had any other consequences. A response to the green light was followed by a mild punishment with complete darkness by switching off all lights for 5 s. After another 3 s, a correction trial followed. A training session lasted for about five blocks, each containing 20 Go and 20 NoGo

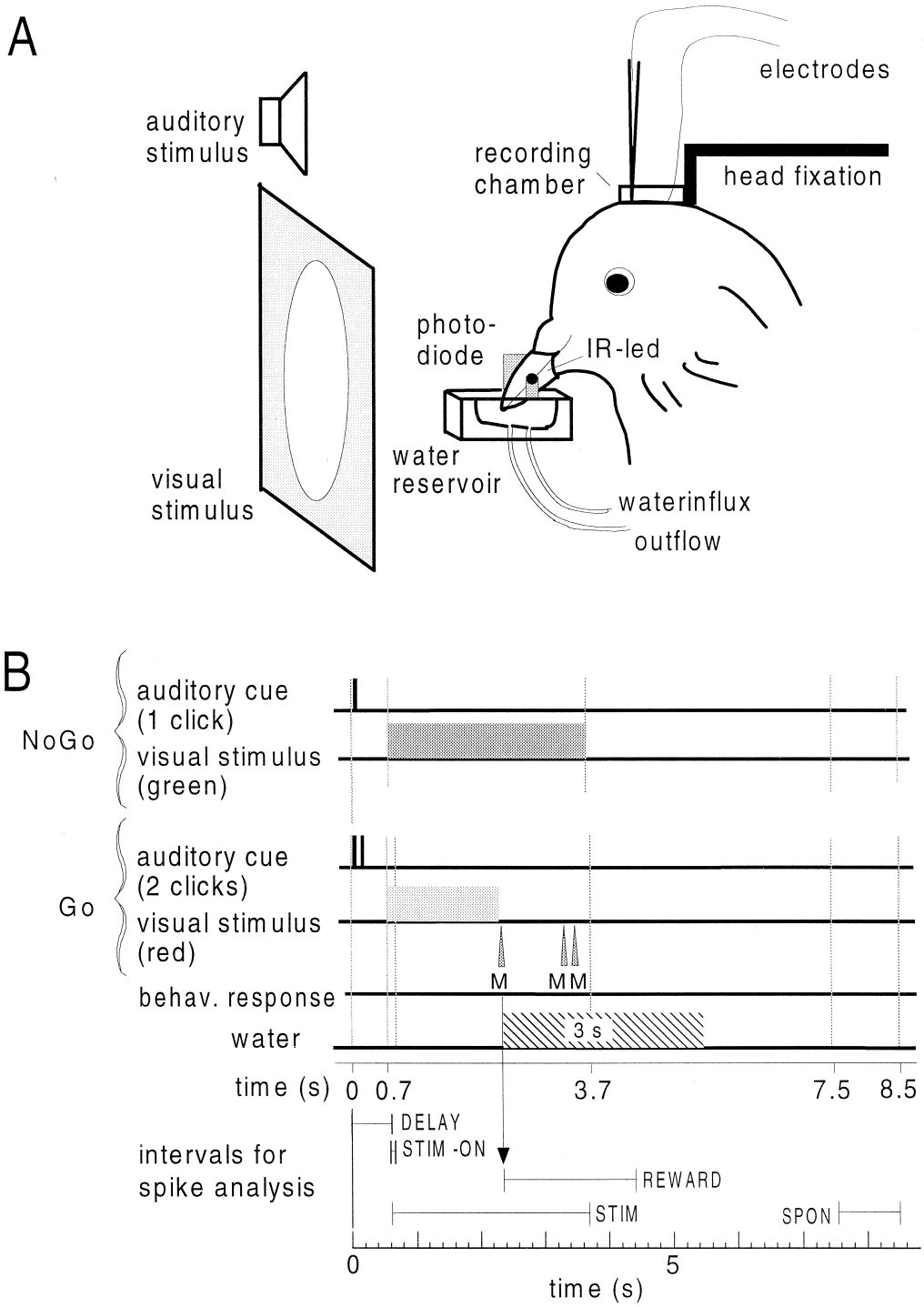

Fig. 1. Diagram of the pigeon in the test situation (A) and temporal sequence in the auditory/visual Go/NoGo discrimination task (B).

trials, that were separated by pauses of about 10 min. Go and NoGo stimuli were presented in random order. After the animal met the criterion of 75% correct responses [(correct GO + correct NoGo)/total number of trials] in three consecutive training sessions, a recording session was interspersed which again was followed by several training sessions. During recording sessions the behavioral paradigm exactly matched training conditions. Correction trials occurring after responding to NoGo stimuli were excluded from analysis of neuronal activity.

Before starting the recording procedures, it was tested whether the animals use the auditory cue presented at the beginning of the DELAY period to form a short-term memory representation of the actual auditory/visual stimulus pair. For this purpose, some 'catch' trials were interspersed in a normal block of training sessions after the

animal had reached a performance level of at least 75% in three consecutive sessions. In a catch trial, the visual stimulus usually presented at the end of the DELAY period was omitted. The end of the DELAY period or the beginning of the response phase, respectively, was indicated by switching on the neutral white light. A catch trial session consisted of 80 trials that incorporated 10 catch trials, five Go trials (double auditory click, no red light stimulation) and five NoGo trials (single auditory click, no green light stimulation). Catch trials were administered every eighth trial in alternating fashion. In order to manage the task, the animal had to remember the auditory cue signal since no information about the stimulus was available during response time. Mandibulation during catch trials had no consequences at all, i.e., there was no reward or punishment in order to prevent learning during catch trials. The behavioral performance in catch trials was calculated separately excluding all trials with double auditory/visual stimulation from analysis. The relative numbers of correct or false responses were subjected to binomial testing.

2.4. Recording procedures

Before each recording session, a 1-mm trephine hole was made over the NCL or adjacent regions and was sealed with bone wax at the end of the recording. Single unit activity was monitored using glass-insulated Pt/Ir electrodes (3–10 μm). Electrodes were advanced through the intact dura with a hydraulic microdrive roughly at an angle of 20° to the vertical plane at a position of A 4.25–7.5 and L 2.5–7.5 according to the atlas by Karten and Hodos [25]. Signals were amplified (DAM 80, WPI), filtered and continuously monitored with an oscilloscope and a loudspeaker. Extracellular signals were recorded during blocks of 20 Go and 20 NoGo trials that were presented randomly. Due to technical limitations data acquisition started 200 ms after the first acoustic click. Neuronal data were stored on a computer (sampling rate 10 kHz) along with markers indicating the click, the start of the visual stimulus, the reward or punishment period and the behavioral responses using commercial data acquisition software (EWB, DataWave). The first 8.5 s of each trial were recorded. Spiking activity was separated on-line from background noise and from movement artifacts during mandibulation and drinking using the built-in window discriminator.

2.5. Data analysis

Recorded spike data were analyzed off-line and isolated into single unit activity using the spike sorting analysis module (EWB, DataWave). In most cases, the activity of one single unit was separated from background noise and only occasionally up to 3 units could be identified at a single recording site. Subsequently, the time of event of the spike was used for analysis. Various histograms were calculated summing the activity recorded under stimulus condition 'red light' or 'green light' separately. Peristimulus time histograms (PSTHs) were generated using the start of each trial as a trigger to look for stimulus-related activity. Additionally, histograms using the time of reward delivery as common origin were applied to look for units whose firing activity was linked to the receiving or expectancy of reward. This was necessary since the behavioral response latencies and hence the time of reward varied to a great extent with regard to the stimulus onset (up to 3 s).

Four different time intervals were defined for the statistical analysis (Fig. 1B). The DELAY interval lasted from 200 ms after the onset of the auditory stimulus to the onset of the visual stimulus. The STIM period enclosed the time from visual stimulation to 3 s later when mandibulation no more elicited reward or punishment. Since a number of neurons showed a time-locked response to the visual stimulus we looked more closely for stimulus related activity by defining a 200-ms interval after onset of the visual stimulus (STIM-ON). A 1-s interval in the intertrial period was used to calculate the spontaneous activity of each unit. Changes in discharge rate during reward delivery were investigated by analyzing a 2-s time interval with the onset of water delivery (REWARD).

Spike counts were normalized to spikes/s. Unit activity was statistically analyzed by comparing the difference scores in every single trial between the spike rate of one of the predefined intervals (DELAY, STIM-ON, REWARD) and the spontaneous spike rate using a non-parametric two-tailed *t*-test for correlated means. Only those units that yielded statistically significant differences in activity ($p < 0.05$) were classified to belong to the particular category under consideration (i.e., STIM, REWARD, etc.). Additionally, *t*-tests were performed on the discharge rates of identical intervals under different stimulus conditions, e.g., red STIM vs. green STIM. Since the STIM-ON and REWARD interval were contained in the STIM interval, a separate analysis of this interval to spontaneous activity was not performed. The entire STIM interval was used for the direct comparison of neural activity in Go vs. NoGo trials. Units with statistically significant differences in activity ($p < 0.05$) under Go vs. NoGo conditions were classified as differentially active.

To check to what extent cellular discharge was correlated to the planning or execution of movement the points in time of mandibulating were used as a trigger for generating correlograms to determine the joint probability of observing a spike X ms before or after the occurrence of a beak movement. Correlograms were calculated only for mandibulation during the intertrial period to exclude the influence of reward related neural activation. Units were considered to be related to premotoric processes if a peak occurred in the 200-ms interval before mandibulation that exceeded the 99% confidence limit calculated from the

average firing rate in the interval of interest under the assumption of statistical independence of interspike intervals (poisson distribution).

The behavioral response of the pigeons, the opening of the beak, and the movements during drinking sometimes caused artifacts during electrophysiological recordings. Waveforms of movement artifacts were characterized by an elongated period and usually had higher amplitudes than typical spikes. These artifacts were eliminated by filtering high amplitude signals using an online window discriminator and an offline spike waveform analysis to separate suspicious long lasting waveforms from spikes signals. The probability of the occurrence of movement artifacts is higher during those periods of the task when the pigeon is forced to mandibulate. Elimination of those artifacts increased the danger of also rejecting simultaneously occurring factual spikes that were embedded in the noise. Thus, elimination of spikes by mistake should have affected mostly the mandibulation or REWARD period. But instead, this is the period in which we found most cells with increased firing rates. Movement artifacts did not contribute to the response characteristics of STIM-ON and DELAY units as only few mandibulations occurred during these periods. Moreover, the majority of these units exhibited decreased spike rates. Hence, we conclude that our findings were only contaminated with movement artifacts to a minor degree which did not affect the general findings.

2.6. Histology

On the last day of recordings, the boundaries within which all electrode penetrations were comprised were marked by inserting a microelectrode stained with the *Dye*I at positions about 200 μm anterior, posterior, medial and lateral to the outermost electrode penetrations [50]. At the end of the experiment, the animals were given an overdose Equithesin and perfused intracardially with saline followed by 4% formalin. The frozen brains were sectioned in a parasagittal plane alternating at 40 and 100 μm, mounted separately and stained with Cresyl violet (40 μm sections) or DAPI (100 μm sections). DAPI stained slices were controlled by fluorescence microscopy and counterchecked with Cresyl violet stained slices to reconstruct the electrode penetration tracks.

3. Results

3.1. Behavioral performance

Testing for working memory was carried out using a group of three animals including one pigeon that was also employed for recording purposes. Without any prior experience with the modified catch trial paradigm these individuals were subjected to behavioral testing. Behavioral performance data were pooled and yielded an overall performance of 21 correct trials out of 30 catch trials (70%). This is clearly above random performance ($p < 0.05$, binomial testing), but lower than in non-catch trials (81%). However, the diminished value may originate from the performance-reducing effect of the extinction condition. Thus, the animals were clearly utilizing the initial auditory stimulus to guide their actions in an appropriate way after the DELAY period. Behavioral performance of those animals that participated in electrophysiological recordings sessions was at a similar level during training sessions and only slightly lower (78%) during the recording sessions.

3.2. Electrophysiological data

A total of 97 units were analyzed for each of which one complete block of 40 Go/NoGo trials was recorded. De-

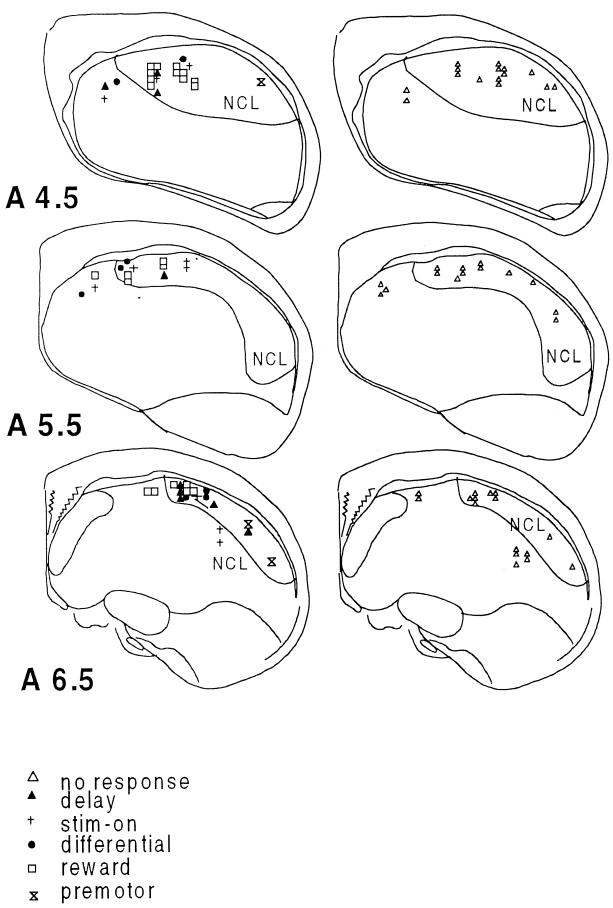

Fig. 2. Location of recording sites of units classified by their response characteristics. Reconstructed recording sites are projected to three representative drawings of frontal sections. The activity of units shown in the sections in the left column were categorized according to the events to which they exhibited significant changes in activity (Table 1; event-related activity) or were summed into the differential class if they only showed differential activity. The locations of units that showed no response are projected to the frontal sections in the right column. Units which responded to more than one event were included in the event category to which the most significant response occurred.

Table 1
Classification of units
Number of units with significant activity changes in the DELAY, STIM-ON and REWARD period. In the case of cells classified as event-related, firing activity in the specified interval significantly different from spontaneous activity. Cells with differential activity showed significantly different firing rates in the specified interval during Go vs. NoGo trials. Comparisons of the activity during the STIM interval to the spontaneous activity were not performed because this interval overlaps the STIM-ON and REWARD period. Since the REWARD interval exclusively occurs during Go trials neuronal activity during REWARD cannot be compared to NoGo trial activity (''–'' = not calculated; see Section 2.5). Some neurons respond to more than one time interval and, thus, categories are not mutually exclusive. The total number of units inside and outside the NCL is shown in parenthesis.

	Inside NCL ($n = 48$)					Outside NCL ($n = 10$)			
	DELAY	STIM-ON	REWARD	STIM	PREMOTOR	DELAY	STIM-ON	REWARD	STIM
Event-related									
Excitatory	2	1	14	–	3	1	1	3	–
Inhibitory	8	9	8	–	–	0	4	0	–
Differential									
Go > NoGo	0	2	–	7	–	0	0	–	2
NoGo > Go	1	1	–	9	–	1	0	–	1

lineating the NCL by the criterion of dopaminergic immunoreactivity as defined by Waldmann and Güntürkün [54], 75 units were located inside the borders of the NCL (Fig. 2). The remaining 22 units were located medial and/or anterior to the NCL. At least, the area ventromedial to the NCL also shows some dopaminergic immunoreactivity so that units in this area, might also participate in NCL functions. Of all units located inside the NCL, 60% (48/75) responded with significant changes in activity during the behavioral task. The same applied to 45% of the cells (10/22) located outside. The response types and the proportion of cells in the four response categories were similar for units located inside and outside the NCL. Most units belonged to the REWARD or STIM categories (Table 1). Although data analyses were performed on all 97 units we will focus on the 75 cells inside the NCL.

3.3. Event-related activity

If mean spike rates in one of the intervals varied significantly from spontaneous activity under identical stimulus conditions this type of response was termed event-related. Cells were classified according to the events at which changes of unit activity occurred, i.e., DELAY units, STIM-ON units and REWARD units. Out of 75 NCL units, 33 units showed event-related activity. Many units responded to only one response category ($n = 25$) but some units belonged to more than one response category ($n = 8$) so that the total numbers of response types does not add up to the number of neurons (Table 1).

3.3.1. DELAY units

Ten units were observed with a change in discharge rate during the DELAY interval. Out of these, 6 units had prolonged depressed firing rates during Go trials whereas 2 units revealed a depressed response in unrewarded NoGo trials. Only 2 units showed excitatory activity in Go trials compared to spontaneous discharge. An example of a delay unit whose peak activity occurred 400 ms after acoustic stimulation is displayed in Fig. 3.

3.3.2. STIM-ON units

All 10 units with STIM-ON related changes of activity were characterized by a decrease in firing frequency dur-

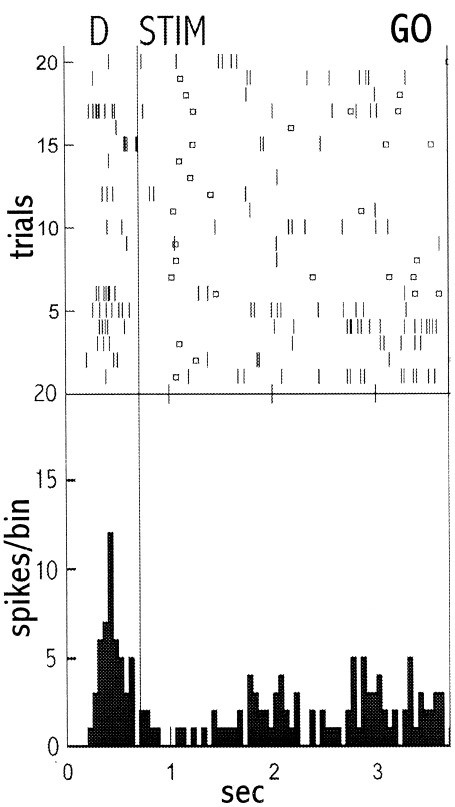

Fig. 3. Raster display and average histogram (bin size 0.05 s) of a unit responding during the DELAY period of Go trials (two-tailed *t*-test, $df = 19$, $p = 0.0364$). The DELAY (D) interval starts after 200 ms when acoustic stimulation ceases. The vertical line indicates the end of the DELAY period and onset of visual stimulation. Each row in the raster display indicates one trial with unit activity shown as vertical marks and behavioral responses (mandibulation) as small open squares.

ing the 200-ms time interval following the onset of visual stimulation. In one case, we saw an excitatory response after the onset of the NoGo stimulus (green light). An example of a unit displaying inhibition starting at the onset of visual stimulation and lasting for about 300 ms is presented in Fig. 4. Behavioral responses to the Go stimulus usually did not occur within this 200-ms STIM-ON interval as can be seen in the dot raster. Therefore, the neuronal activity during this period most likely was stimulus driven and not related to mandibulation or reward. In addition, in six out of 10 cases neuronal activity returned to baseline during the REWARD period following the 200-ms STIM-ON interval indicating that these units were responding to the onset of the visual stimulus.

3.3.3. REWARD units

Reward-related activity was defined as a neuronal response during reinforcement. The time of reward delivery varied in each trial due to the differences in the animal's response latencies. After realigning the spike activity to the onset of reward 14 units turned out to have increased and 8 units decreased firing rates during the REWARD interval. Reward related responses were characterized by a change in activity, either excitatory or inhibitory, starting with the reward (Fig. 5) and lasting for the duration of the REWARD interval. During the REWARD period, there was no obvious correlation between beak openings and the neuronal discharge pattern. Instead the delivery of liquid led to a long lasting stable neuronal response that sometimes exceeded the actual period of liquid consumption.

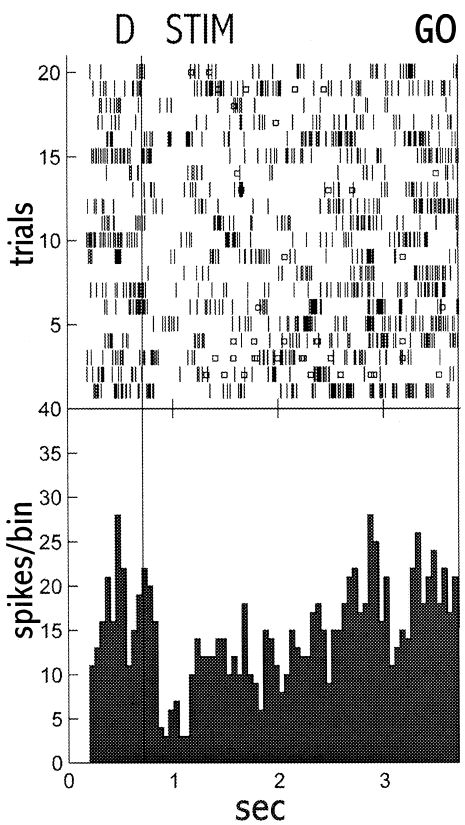

Fig. 4. Raster display and average histogram (bin size 0.05 s) of a unit exhibiting an inhibitory response to the onset of the visual stimulus (two-tailed *t*-test, $df = 19$, $p = 0.018$). The vertical line marks the onset of the visual Go stimulus, which immediately is switched off if mandibulation occurs during the STIM interval. Each row in the raster display indicates one trial with unit activity shown as vertical marks and behavioral responses (mandibulation) as small open squares.

Since the pigeons were well trained and therefore made only few mistakes during the NoGo stimulus presentation, the number of erroneous trials was not sufficient to analyze the neuronal response after mandibulation in NoGo trials. Thus, a direct comparison of neuronal activity after correct and incorrect behavioral activity was impossible.

Three of these reward-related units could be regarded as reward expectancy units. Their response pattern was slightly different from that of typical reward units as their activity increased starting about 500 ms before the delivery of reward instead of shortly after the onset of reward (Fig. 6). Out of these, 2 units exhibited elevated firing rates that lasted for a long time so that high discharge rates were maintained throughout the reward delivery period when the visual stimulus was no longer present. Most important, none of these units exhibited this kind of activity when the animal mandibulated outside the context of a trial sequence. Thus, in these neurons, changes in spike rates were observed only in the histograms aligned to mandibulation prior to reward but not when aligning spike activity to mandibulations that occurred in the intertrial period. Moreover, these neurons did not display significant changes in firing rates during the STIM-ON interval. Hence, it is very unlikely that the activity of these units was related to the visual stimulus or had preparatory motor functions.

In Fig. 6A, a unit's response is depicted during one of the rare cases of poor behavioral performance (only six correct Go trials out of 20). This is a particularly convincing example of a clear relation between the behavior of the animal and the response of a neuron. Discharge rates were augmented only in Go trials with correct behavioral responses (dot raster). The PSTH with a starting point at time zero and, thus, aligned to the visual stimulus remained mostly flat whereas the histogram realigned to reward (R) and containing only the correct trials revealed event related activity changes. Additionally, there was no correlation of neuronal activity and mandibulation outside the STIM interval, thus, excluding the possibility that enhanced activity is merely related to beak movement.

The activity of the cell shown in Fig. 6B was recorded while the pigeon responded correctly during all 20 Go trials. The firing pattern of this unit was characterized by prolonged bursts before and during mandibulations that were timed around the REWARD period. In contrast, mandibulations during the intertrial period were not accompanied by comparable spike trains. In the remaining reward expecting cell, spiking ceased before the reward

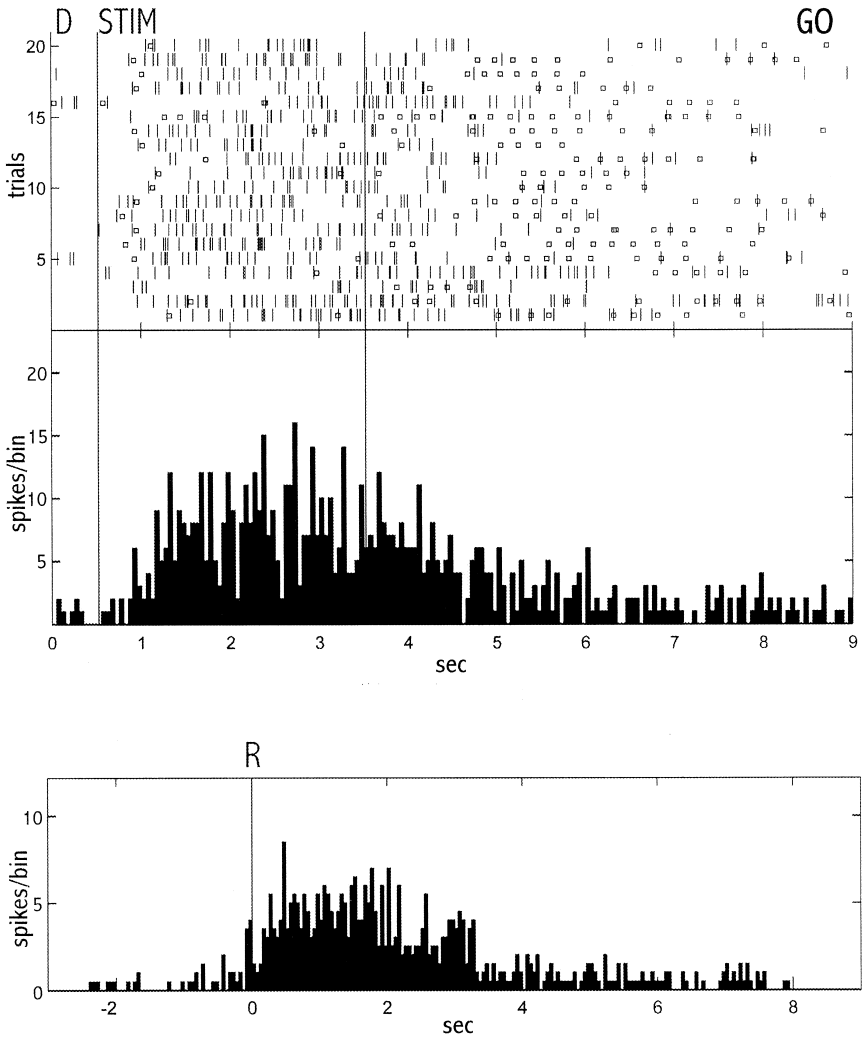

Fig. 5. Unit with reward related activity (two-tailed *t*-test, $df = 19$, $p < 0.001$). Both the top raster display and the histogram below are aligned to stimulus presentation. The histogram at the bottom is realigned to the onset of reward.

was delivered to the animal. As in the other two examples, excitatory responses were observed only if mandibulation occurred during the STIM period and led to reinforcement.

3.4. Premotor units

Three units exhibited elevated firing frequencies prior to beak movements outside the STIM interval. Mandibulations during the STIM period were excluded from analysis to prevent interference with activity changes related to the delivery of reward. Peaks in the correlograms (calculated as outlined in Section 2) usually occurred around 70 to 80 ms before beak movements (Fig. 7) and were broad with a half width of approximately 30 ms. Secondary peaks in Fig. 7 are due to volleys of mandibulating movements (3–5 mandibulations at approximately 5 Hz) and reflect activity to beak movements adjacent in time. Premotor units were located in the more lateral aspects of the NCL. In one case, a premotor unit exhibited additional changes in firing frequency to a second event, that is the DELAY period. No purely sensory driven activity could be detected in premotor units during both Go or NoGo trials.

3.5. Differential responses to Go and NoGo trials

In case of significant differences in discharge rates of the same interval under different stimulus conditions (Go(red) vs. NoGo(green)), the activity was defined to be differential. Statistically significant differences in spike rates between Go and NoGo trials were observed for several NCL neurons ($n = 19$) either in the DELAY, the STIM-ON and/or the STIM interval (Table 1). One neuron showed a differential response during the DELAY and STIM interval (number of differential responses = 20).

Only 1 unit had significantly higher spike rates during the DELAY interval in response to the NoGo stimulus than to the Go stimulus. Another set of 3 units responded differentially to Go and NoGo stimuli during the STIM-ON interval. None of these cells showed a differential response during the DELAY interval.

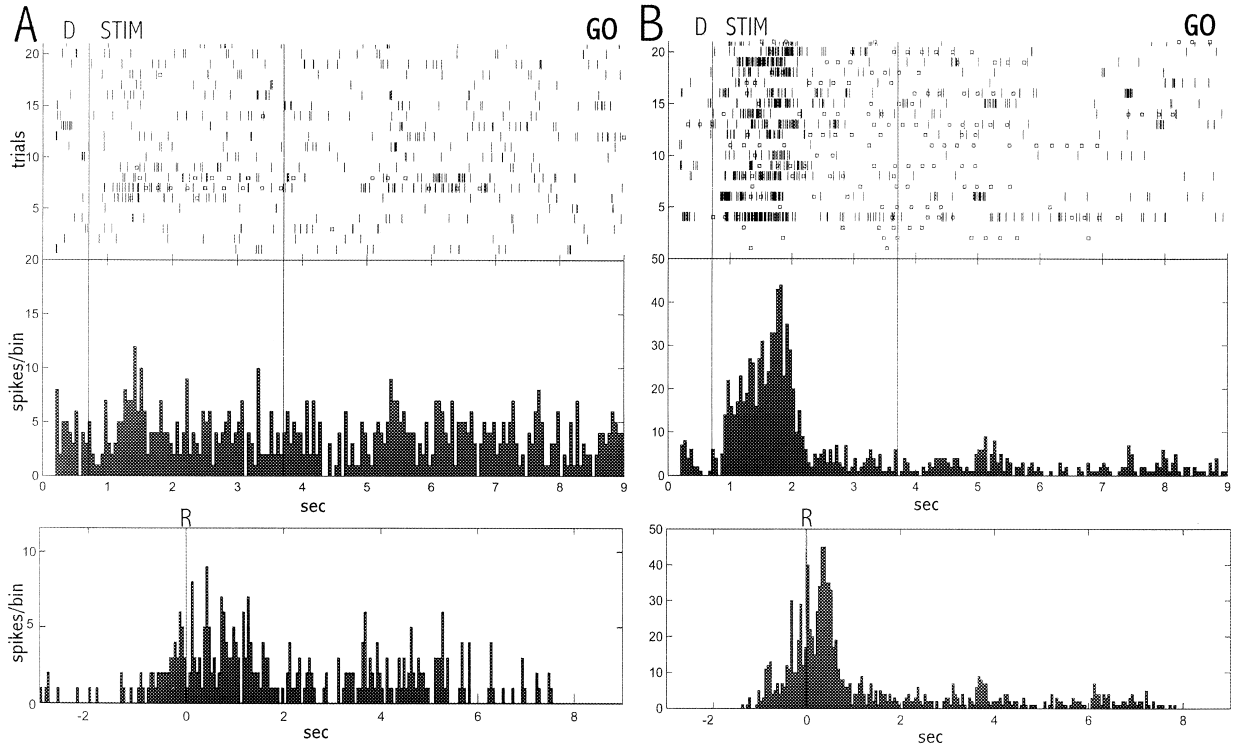

Fig. 6. Examples of reward-expectancy units. The top raster display and the histogram below are aligned to stimulus presentation and the histogram in the bottom row is realigned to the onset of reward. (A) The raster display reveals augmented discharge only in trials with correct behavioral response. The rearranged histogram shows the neuronal response starting before the onset of reward delivery (zero) (two-tailed *t*-test, $df = 19$, $p = 0.033$). (B) Excitatory response with burst-like discharge pattern (two-tailed *t*-test, $df = 19$, $p = 0.005$). The rearranged histogram illustrates that the neuronal activity starts as early as 800 ms before reinforcement onset.

Significant changes in spike activity between Go and NoGo trials were observed most often during the STIM interval. The STIM interval comprised part of the period of liquid delivery and consumption. Seven neurons showed increased spike rates during the Go STIM period compared to the same interval under the NoGo condition whereas nine neurons exhibited enhanced activity during the STIM interval in NoGo trials. One example of differential activity during the STIM period is shown in Fig. 8. This unit exhibited prolonged depression of the firing rate that nearly

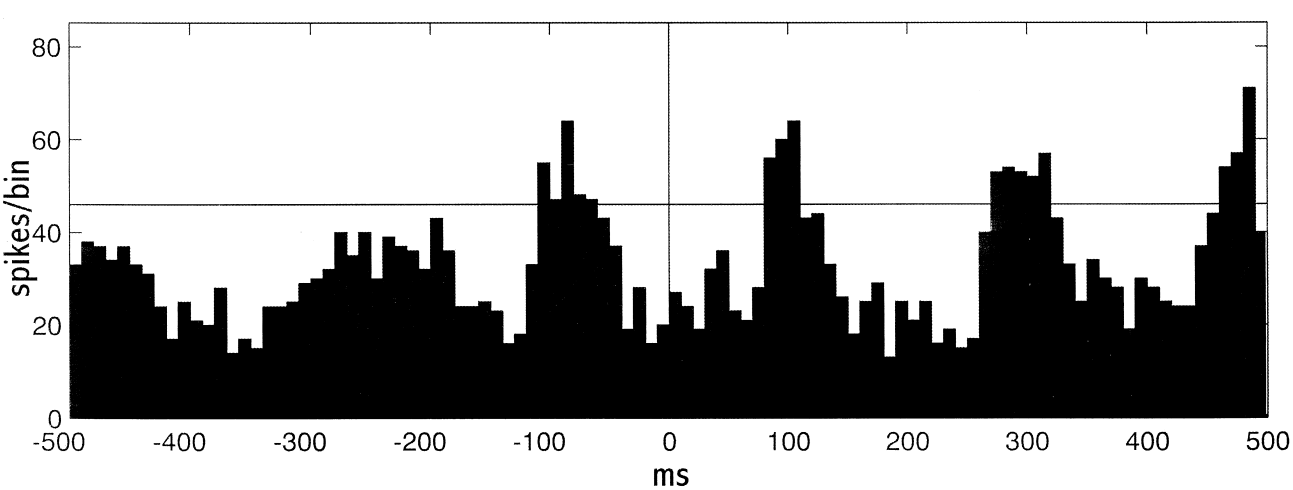

Fig. 7. Single unit activity correlated to motor behavior. Mandibulations take place at the origin of the abscissa. The horizontal line depicts the 99% confidence interval of spike counts under the assumption of a poisson like distribution of interspike intervals. The activity peak around 80 ms prior to beak movement is characteristic of premotoric activity, all other peaks are due to mandibulating in rapid succession.

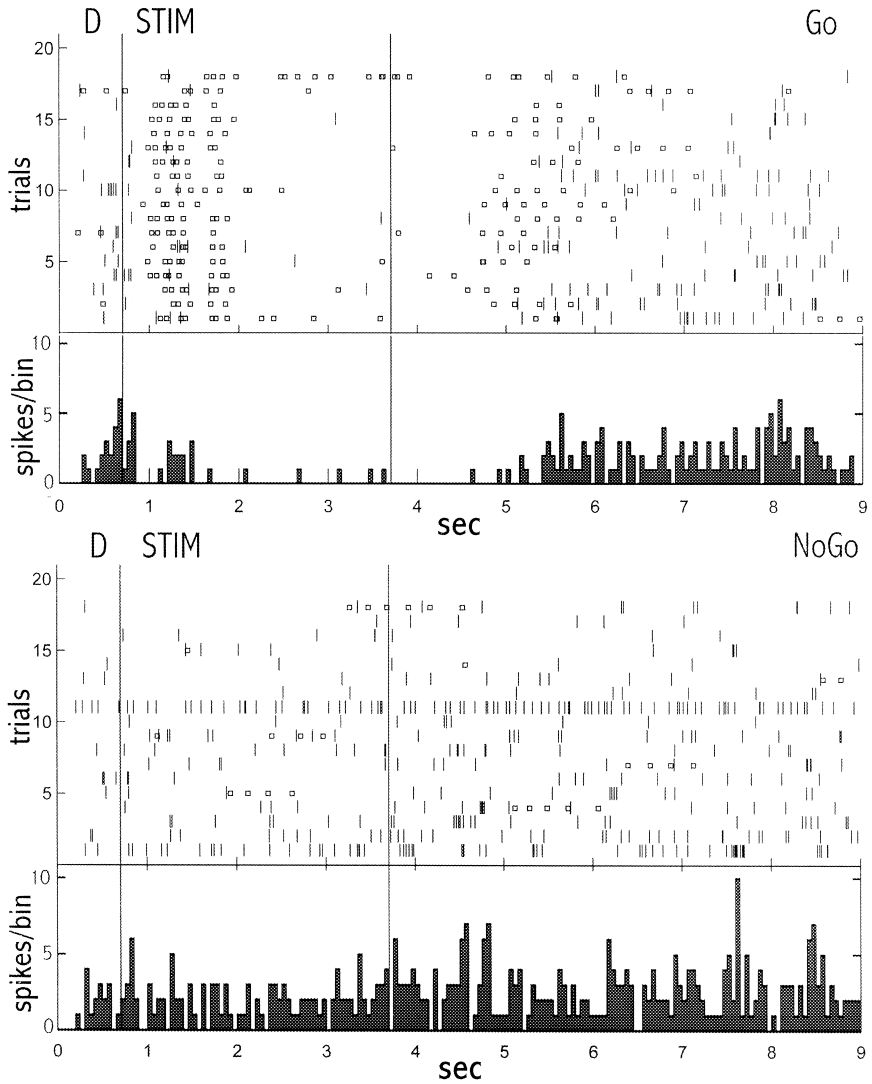

Fig. 8. Activity of a unit responding differentially to Go and NoGo trials. The upper raster and histogram displays show the Go trials, the lower histograms show the NoGo sequences. The unit is inhibited during the STIM period of Go trials as compared to NoGo trials (two-tailed *t*-test, $df = 19$, $p = 0.004$). The level of performance in the behavioral task for the animal in this particular Go/NoGo sequence was 85%.

dropped to zero when the red Go stimulus was presented. No obvious alteration of the discharge pattern appeared in corresponding NoGo trials. In the Go trials, the stimulus light was turned off as soon as the animal opened its beak for the first time but the depression of firing rates sustained even though the visual stimulus was no longer present. This differential activity cannot be attributed to the different physical properties of the visual stimuli and might indicate that the event and not the stimulus as such was coded.

Since there is some overlap between the REWARD and the STIM interval, reward related activity that, by definition, exclusively occurs in Go trials could mimic differential activity during the STIM interval. However, only seven out of 19 neurons with differential activity during the STIM period additionally exhibited firing changes related to the reward. In all other instances, differentially significant activity was not accompanied by event related activity in the STIM-ON or REWARD period. Therefore, differential activity during the STIM interval is very likely not a tautological description of reward related elevated/depressed firing rates in Go trials compared to unchanged activity in the corresponding NoGo interval. The example of differential activity in Fig. 8 underlines this notion since the activity changes during the STIM interval are not time locked to the reward or onset of the visual stimulus. Units with premotor activity were not included into this analysis because differential activity most likely is due to the higher degree of motoric activity during the STIM period in Go trials compared to NoGo trials.

3.6. Neuronal activity and behavioral performance

All response types described above represent distinct sequences of the behavioral task and might provide the

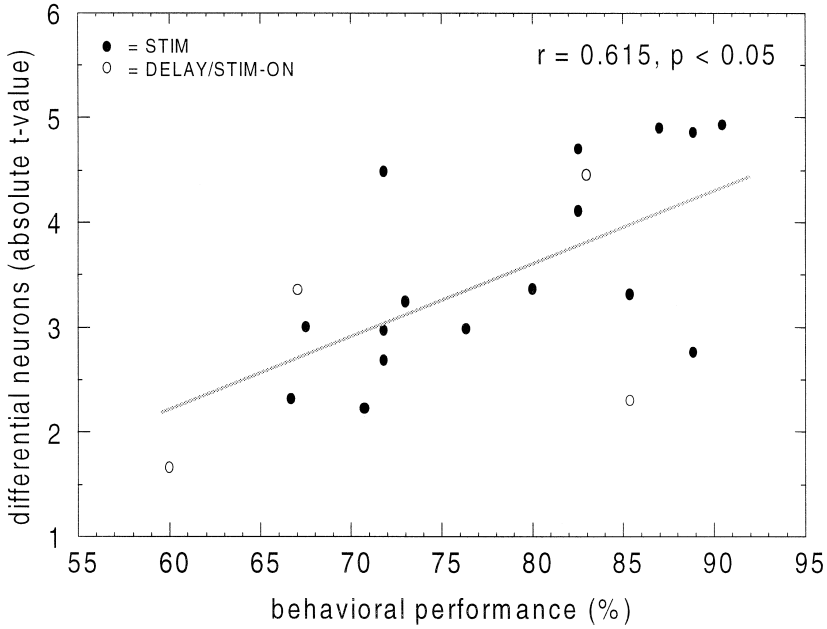

Fig. 9. Regression between the level of performance in the behavioral task and the *t*-values of the differential neuronal activity of units that were recorded during these Go/NoGo sequences ($n = 20$, $r^2 = 0.615$, $p < 0.05$). The level of performance was calculated as ratio of correct responses to total number of trials [(correct Go + correct NoGo)100/total number of trials]. The absolute *t*-value of the two-tailed *t*-test of the differential neuronal activity calculated for the STIM (closed circles) or the DELAY and STIM-ON (open circles) is projected to the ordinate.

neural basis for the acquisition and execution of the task. However, activity time-locked to certain events of the task is not sufficient to explain discriminative behavior. If pigeons perform well in this task they must be able to distinguish between Go and NoGo trials and one might expect a correlation between neuronal discriminative ability and the behavioral performance. A measure for the capability of a neuron to distinguish between Go and NoGo trials is the *t*-value which is the test value of the non-parametric *t*-test which compared spike rates of identical time intervals under different stimulus conditions. A measure for the behavioral performance is the ratio of correct responses to the number of trials. To relate the activity of NCL neurons to the behavior during the Go/NoGo task we performed a correlation between the *t*-values ($n = 20$) of all differentially responding neurons and the behavioral performance during the corresponding blocks of 40 Go/NoGo trials (Fig. 9). For the differentially responding neurons, there was a positive correlation between variations of firing rates to Go vs. NoGo trials and the percentage of correctly accomplished trials ($r = 0.615$, $p < 0.05$). Thus, the better the ability to discriminate the stimuli the higher the probability of measuring a large difference of spiking activity for Go trials compared to NoGo trials.

4. Discussion

Our results indicate that cells in the NCL of pigeons respond to specific events of an auditory/visual delayed Go/NoGo task, react differentially to the behavioral significance of the stimuli and exhibit neural activity patterns correlated to the operant behavior. Differentially responding neurons were characterized by increased or decreased firing rates when comparing corresponding intervals of neuronal activity in Go trials vs. NoGo trials (Fig. 8). Some units were selectively activated or depressed during the delay phase (Fig. 3), reward related units, the most frequently observed category, responded to water delivery (Fig. 5), while others seemed to signal expectancy of reward (Fig. 6B). Cells responding to the visual stimulus (Fig. 4) and those showing increased activity before the operant behavior to be executed (Fig. 7) complete the picture of the NCL as a multimodal association area that participates in the generation of goal directed behavior and bridges the gap between stimulus delivery and behavioral execution. The present data therefore clearly support the hypothesis that activity patterns of NCL-neurons are modified according to the learning history of the animal and play a critical role in planning and executing behavioral outputs.

4.1. Working memory

Typical working memory tasks include a DELAY period that requires to store information temporarily in order to execute the correct response after delay offset. Our behavioral paradigm also included a DELAY with no stimuli present. However, we used a modified procedure in which the auditory cue before the DELAY period and the visual stimulus thereafter both and independently from

each other signaled the Go- or the NoGo-character of the trial. This paradigm was used since it considerably reduced the otherwise very long training times of the pigeons. In case of this redundant double stimulation, there is no need to rely on working memory since attending to the second visual stimulus is sufficient to manage the task. However, an experiment performed beforehand with interspersed catch trials had shown, that the animals actually had stored a representation of the auditory stimulus in working memory. These trials afforded working memory usage since the visual stimulus was omitted. Unrewarded catch trials exclude the possibility that the animals learn and apply a different strategy than they do in the behavioral paradigm used in all other sessions including recording sessions. As expected for trials performed under extinction conditions, behavioral performance during catch trials was lower than during reinforced conditions but was still well above chance level. Thus, the animals had formed a memory representation of the auditory cue to correctly guide their postdelay actions. Since the frequency of catch trials needs to be very low it is not possible to sample a sufficient quantity of neuronal data necessary for the applied analyses and hence, recording of single unit activity was not performed in catch trial sessions.

During the subsequent recording sessions we observed changes in firing rates during the DELAY period in 10 units. Neuronal responses lasted several hundred milliseconds and exhibited their maximum or minimum activity usually about 400 ms after the acoustic stimulation. These response properties are clearly in favour of a working memory related neuronal component rather than a sensory representation of the acoustic stimulus. Thus, the delay units could represent an important part of the cellular basis of working memory performance in pigeons.

To our knowledge, this is the first time single unit activity related to working memory was reported in avian species. Based on the current data it is difficult to infer what kind of information is encoded in the activity patterns occurring during the DELAY period. Sophisticated experimental procedures were used to elucidate this issue in primates. There is convincing evidence that neuronal activity in primates is not merely an unspecific activation but really conveys stimulus specific information [33], as discharge patterns during delay varied consistently with stimulus features in a spatial oculomotor delayed response task [11] and led to the concept of memory fields [17,40] that were introduced in analogy to receptive fields of sensory neurons. Experiments with pairs of stimuli presented in succession, in which the same stimulus had different associative significance depending on the context of the previously presented stimulus revealed, that at least part of the PFC units encode the behavioral significance of a stimulus, that is, they exhibited different discharge rates to the same stimulus depending on the behavior to be executed [55].

In our study, the majority of delay related units exhibits depressed activity compared to spontaneous discharge. Though sustained depressed firing rates are a common feature of short-term memory related neuronal activity in mammals [4,39] the fraction of neurons exhibiting augmented discharge rates is clearly higher in primates compared to our data. This variance could be related to the response inhibition of a planned behavior which the pigeons had to perform and not to the representation of certain stimulus features to be remembered. However, at least in primates response inhibition during NoGo trials can be associated with augmented firing rates in PFC [56]. Thus, the primarily depressed firing rates might be a peculiarity of the avian NCL.

4.2. Behavioral relevance of NCL activity

The behavioral paradigm employed in this study requires several cognitive capabilities in order to manage the task successfully. Besides learning to associate arbitrarily chosen stimuli with certain behaviors the animal has to hold information in working memory to bridge the DELAY period introduced in between stimulus presentation and response initiation. A third prerequisite is the ability to suppress behavioral responses during NoGo trials. Since lesion studies have shown that damaging the NCL is detrimental to working memory [14,20,34] and Go/NoGo performance [20,22] this structure obviously participates in short-term memory and behavior sequencing. The present study shows that NCL neurons are able to code for each part of the relevant cognitive aspects of these tasks.

One of the recorded cells which supports this conclusion is the reward expectancy unit shown in Fig. 6A, in which augmented firing rates only occurred in cases of correct behavioral responses and well after the end of the DELAY period. The neuronal responses starting before the onset of the reinforcement were definitely not related to sensory processing as there was no external event that could have elicited this change in firing rate. Since these changes in spike activity exclusively occurred before the behavioral response leading to reward was executed, these units might predict the upcoming reward and might be used to prepare for the consumption of liquid. Similar patterns of single unit activity are observed in delay tasks in mammals and are thought to be related to response initiation. This kind of activity is referred to as scalloping and occurs in excitatory as well as inhibitory neurons [5,33].

In order to generate goal directed behavior like in the employed Go/NoGo task the pigeon has to form a neural representation of behaviorally significant stimuli presented in various modalities. The NCL is suited to participate in this function due to its afferent connections from multiple secondary sensory areas [28,49,59]. Afferent fibers from different sensory modalities project to certain subdivisions of the NCL with considerable overlap which is probably related to cross-modal integration of sensory input [27]. Closely linked to cross-modal sensory integration is the

ability to discriminate between the arbitrarily chosen stimuli. Neurons that fire differentially to the stimuli might be well suited for this purpose. Several of the recorded units showed differential activity between Go and NoGo trials in the short interval right after the presentation of the stimulus (STIM-ON) or during the whole STIM interval without any external event to which this change in activity was attributable (Fig. 8). Those activity patterns might subserve the discrimination of stimuli or build up a representation of their behavioral significance. Based on the experimental data, it is currently not possible to unambiguously reject the assumption that these cells are encoding purely sensory stimulus properties. However, two observation are in favour of a contribution of these neurons in representing relevant events rather than sensory characteristics. This conjecture is emphasized by, first, the loose time coupling of some differentially firing units to external events or motor behaviors, and, second, by the correlation between the behavioral performance and the t-values (Fig. 9), as a measure of the individual neuron's capability to discriminate between the presented stimuli. This issue has been investigated in primate PFC where single units have been demonstrated to reflect the behavioral significance of stimuli and not merely their physical properties [55,61].

In the present experimental paradigm, the behavior to be executed in order to receive reward is to open the beak. Hence, if the NCL is engaged in the planning of goal directed behavior there should be neural activity that is correlated with mandibulation. The premotor units might be engaged in the planning of the upcoming response since they increased their firing frequency before mandibulation in a timely correlated fashion. The broad activity peaks preceding the movement by 70 ms might reflect a rather loose coupling of NCL activity to motor behavior. Detailed motor commands that exert influence on individual muscles are likely to occur in neural structures that are situated more downstream in the hierarchical framework of sensory-motor integration like the basal ganglia and the archistriatum which both receive afferents from the NCL [27,28,62].

A prerequisite for learning to generate the appropriate motor output to the different stimuli is to evaluate the consequences of the executed behavior. Reward related units (Fig. 5) might play an important role in this process. Again, it is not possible to decide whether the reward related units encode the somatosensory or gustatory properties of the received reward or are involved in reinforcing successful behavior. However, in some units, the response to the delivery of reward exceeds the time during which liquid was actually available (Fig. 5). This contradicts a predominantly sensory function of these cells.

Reward related responses are likely to be mediated by the dopaminergic input to the NCL via midbrain VTA neurons. The modulatory neurotransmitter DA is thought to be involved in various forms of learning in mammals and birds [2,19,51] and possibly plays an important role in the acquisition of cognitive tasks, like Go/NoGo and working memory. The NCL receives a massive dopaminergic input [10,32] and thus functions and firing patterns are very likely affected by DA. Effects of DA on working memory are well established in mammals and there is considerable evidence for DA being involved in these tasks in birds as well [21,38,58]. Besides a role for DA in enabling to maintain a stimulus representation in working memory [21] DA is thought to participate in reward mediated learning processes and is especially active in circumstances when the outcome of a situation deviates from the predictions the animal made relying on former experience [29,48].

4.3. Electrophysiological similarities between PFC and NCL neurons

Electrophysiological properties of NCL units resemble in many aspects those of cells found in the PFC. Prefrontal units with altered firing rates during the DELAY period spanning the time from stimulation offset to response onset, are believed to form the neural basis of working memory [12,16]. NCL units in pigeons with significant activity changes in the DELAY period (Fig. 3) are probably comparable to those PFC neurons and subserve similar functions.

Another class of neurons that share similar response properties common to PFC cells are the units that enhanced their activity before the presentation of reward. The reward expectancy units described by Markowitsch and Pritzel [31] and Watanabe [57] start to show elevated firing rates several seconds before reward is delivered and are thought to be related to preparatory set. Although the time interval NCL unit activity precedes the onset of reward is much smaller (< 1 s) than in primates the units seem to share the same anticipatory functions.

Sensory neurons similar to the kind of units we observed have also been found in the PFC. There are units whose discharge rates change time-locked to the presentation of stimuli and that react to stimuli in a differential manner (Fig. 4) [39]. Watanabe [55,56] reported different types of sensory neurons that encode physical stimulus properties as well as the behavioral significance of a stimulus.

The existence of reward related units is a key feature of the mammalian PFC and prefrontal neurons that react to the presentation of reward with augmented spiking activity have been described in numerous studies [39]. Reward related activity was also the type of response found most frequently inside the NCL. Hence, the NCL of the pigeon is likely to be engaged in the processing of reward related information in a fashion similar to the PFC. Dopaminergic tegmental neurons are known to be involved in the processing of reward [29]. In primates, these cells have been shown to signal the amount of discrepancy between the expected and the observed outcome of a learned response

[47]. This type of activity closely resembles core aspects of the Rescorla–Wagner [43] learning theory which requires a system to detect unexpected results of its own learned responses. Reward neurons may thus constitute an essential compound of the NCL architecture to adapt to the changing requirements of complex stimulus–response relationships.

In many PFC studies, inhibitory responses to different events of a delay or Go/NoGo task are reported [39,44,61]. The fraction of inhibitory neurons seems to be smaller in the PFC than in the NCL but nevertheless inhibition of firing rates in response to certain events seems to be a common feature of NCL and PFC neurons. Functionally, the predominance of inhibitory responses could be linked to the usual observation that PFC-lesions and especially those of the orbital area lead to a massive disinhibition of behavior. The breakdown of Go/NoGo-performance in prefrontal animals is therefore often not due to a decrease of missing responses during Go-, but due to a dramatic increase of false alarms during NoGo-trials [12,44,45]. This was also the case in the work of Güntürkün [20] in which NCL-lesioned animals had deficits in response withholding leading to a significantly decreased Go/NoGo-performance.

So far, only few premotor units have been found that tend to be located in the more lateral aspects of the NCL. Since there is a prominent efferent projection from the NCL to the archistriatum one would expect to find more motor related activity inside the NCL. Perhaps units with premotor response properties are located in the deeper areas of the NCL which mostly have been spared in this study. However, it is also likely that premotor functions are generated in one of the several archistriatal subdivisions to which the NCL is known to project [27,32,46]. If this is the case, the non-motor part of complex behavioral sequences would be planned and controlled by NCL units, while the planning and execution of the final motor output would be processed within the archistriatum.

Many response types discussed above are not unique to the PFC. In mammals, activity changes similar to those observed in the PFC have also been found in the temporal and parietal cortex and striatal areas [1,23,36]. Although it is not clear whether the response specificity is generated separately in these cortical areas or whether it is distributed via intratelencephalic connections it is evident that there is a substantial overlap in function concerning these forebrain areas. In the pigeon, neurons with task-related activity were located inside NCL but also in the area close to NCL but outside its borders as defined by Waldmann and Güntürkün [54] according to the density of dopaminergic innervation. This structural delineation is not as sharp as the cytoarchitectonic features on which the anatomical definition of the PFC rests [60]. Cells located adjacent to the NCL might contribute to the processing of task specific information as this area receives at least a diffuse dopaminergic innervation.

4.4. Correlation of behavior and unit activity

We applied a straightforward method of analyzing the correlation of the behavioral performance of the animal and the extent of differential neuronal discharge during Go and NoGo trials. Using this approach, we bypassed the problem that our experimental design did not allow to clearly distinguish whether differences in neuronal activity between Go and NoGo trials were due to the altered sensory input or to the concomitantly changing behavioral response. To dissociate stimulus related neuronal activity from that related to behavior, it would be necessary to compare, for example, the cellular discharge pattern in correct and erroneous trial under identical stimulus conditions, i.e., to compare PSTHs of correct Go trials to those of incorrect trials. However, since the number of erroneous trials in a block of 40 trials was too low this analysis could not be applied to the current data set.

The positive correlation between the behavioral performance and the difference of spike activity between equal intervals during Go and NoGo trials does not necessarily imply a causal relationship between the activity of a single neuron and the behavior of the animal. Rather, it indicates that in the population of differentially activated neurons, a large number of correctly accomplished trials is accompanied by an increase of the neuronal discrimination scores (t-values). Population coding schemes propose that in neural tissue information is encoded by the activity distribution of a neural population and can be retrieved by specific averaging procedures [53,63] that take into account the activity of all participating units. Spike rate differences of randomly chosen representatives of a neural population are used here to estimate whether the activity distribution of the population as a whole varies in accordance with the behavioral performance of the animal. If the differentially responding units participate in the encoding of the behavioral significance (correct vs. incorrect) of the stimuli, differing firing rates are likely to emanate more frequently in case of appropriate behavioral responses.

5. Conclusions

The different types of single unit activity found in this study can be attributed to different aspects of an auditory/visual Go/NoGo task, i.e., representation of the stimuli (stimulus related activity), keeping up a representation of the stimulus over time (working memory, delay related activity), expectation of reward (reward expectancy), preparation for response (premotoric activity) and feedback of the consequences of the executed behavior (reward related activity). Behavioral studies have stressed the importance of the avian NCL in several cognitive tasks like delayed alternation and reversal learning [22,14,34,35]. Lesions of the NCL lead to impairments in the aforementioned tasks without affecting sensory discrimination per-

formance, thus, underlining the contribution to cognitive functions of this area. These data corroborate the hypothesis that the NCL is part of the neural network that enables the pigeon to generate goal directed behavior and perform cognitive tasks as demonstrated in the applied Go/NoGo paradigm.

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