



Grouping subjects based on conditioning criteria reveals differences in acquisition rates and in strength of conditioning-specific reflex modification

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ABSTRACT

Averaging behavioral data such as the nictitating membrane response (NMR) across subjects can conceal important individual and group differences. Analyses were conducted of NMR data from rabbits that were grouped based on the point during NMR conditioning when subjects produced 8 conditioned responses (CR) in a set of 10 trials. This resulted in five groups (Early Day 1, Late Day 1, Early Day 2, Late Day 2, Early Day 3) in which group differences in CR acquisition rates were found. Percent (%) CRs were not found to increase monotonically and between-session differences in % CR were found. Conditioning-specific reflex modification (CRM) of the NMR is a type of enhanced reflexive responding of the NMR that is detected when the unconditioned stimulus (US) is presented in the absence of the conditioned stimulus (CS) following paired classical conditioning. CRM occurred in some subjects in all five groups. Subjects from both the group that was fastest and the group that was slowest to reach the learning criterion had unconditioned response (UR) topographies following NMR conditioning that strongly resembled the CR-UR response sequence elicited during NMR conditioning. This finding was most pronounced when the US duration used to assess CRM was equivalent to that used during NMR conditioning, further evidence to support the hypothesis that CRM is a CR that has generalized from the CS to the US. While grouping data based on conditioning criteria did not facilitate identifying individuals more predisposed to exhibiting CRM, strong CRM only occurred in the groups that reached the conditioning criterion the fastest.

1. Introduction

Schreurs, Oh, Hirashima, and Alkon (1995) reported that following robust nictitating membrane response (NMR) conditioning using a delay paradigm with a tone conditioned stimulus (CS) paired with an aversive electrodermal stimulation (ES) unconditioned stimulus (US) to the periorbital area, exaggerated responding to the US occurred when the US was later presented to the rabbit in the absence of the CS, a phenomenon termed conditioning-specific reflex modification (CRM). This exaggerated reflexive responding includes an increase in unconditioned response (UR) amplitude and area and a shift to later UR peak latencies than the rabbit exhibited prior to CS-US pairings. The basic CRM experiment is an ABA design where the baseline level of responding to USs of varying intensities and durations is assessed prior to (Pretest) and following (Posttest) NMR conditioning. CRM is associative in nature and has been found to be “conditioning-specific” because while it is observed in rabbits receiving CS-US pairings, it is not observed in sit control rabbits, nor in those given explicitly unpaired CS and US presentations (Schreurs et al., 1995). Gruart and Yeo (1995) and

Wikgren and Korhonen (2001) have also reported enhanced reflexive responding to the US following classical conditioning of the NMR in rabbits.

Early observations of CRM noted the striking similarity between the topography of the UR and the CR following conditioning. More specifically, Gruart and Yeo (1995) and Schreurs et al. (1995) found that following CS-US pairings, the topography of the NMR during US-alone trials closely resembled topographies of the CR-UR response sequence elicited during acquisition, particularly at US intensities milder than the training intensity. From Pretest to Posttest, the UR developed from a uniphasic response to a multiphasic response with an increased amplitude and area. Additionally, on Posttest the UR peaks shifted later from US onset toward the point where the US would have occurred had the US-alone trial been a CS-US trial. For example, Schreurs, Smith-Bell, and Burhans (2011a) found that rabbits given CS-US pairings had significantly later peak latencies on Posttest at both 0.25-mA and 0.5-mA, with peaks occurring ~200 ms following ES-onset, than they exhibited on Pretest, with peaks occurring within ~100 ms of ES onset. These changes in the basic NM reflex suggest that the conditioning-specific

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changes in the UR observed on Posttest, particularly at intensities milder than the training intensity, may be due to the UR becoming a CR that has generalized from the CS to the US (Gruart & Yeo, 1995). In other words, the US may be triggering the generation of the response pattern that normally was elicited to the CS during CS-US pairings (Schreurs et al., 1995).

Additional evidence in support of the CR generalization hypothesis is that the strength of CRM was found to be a function of the strength of NMR conditioning. More specifically, manipulations that produced greater NMR conditioning levels or rates also increased the strength of CRM (Burhans, Smith-Bell, & Schreurs, 2008). For example, while one day of CS-US pairings resulted in a low level of NMR conditioning (17% CRs), both three and six days of CS-US pairings resulted in levels of conditioning in excess of 90% CRs (Schreurs et al., 1995). CRM was not observed in the one-day group, only a UR peak latency shift was observed on Posttest in the three-day group and the most robust CRM was observed in the group receiving six sessions of NMR conditioning. In another study, 1-mA, 2-mA and 4-mA periorbital ESs were found to support increasing rates of NMR conditioning while consequently increasing CRM strength (Seager, Smith-Bell, & Schreurs, 2003).

However, additional studies suggested that although CRM may share similar associative processes with the CR, the two can also be dissociated, indicating that CRM cannot be fully explained by the generalized CR hypothesis. For example, Schreurs, Shi, Pineda, and Buck (2000) found that CRs and CRM do not extinguish similarly. While CRs extinguished well in rabbits presented with six sessions of CS-alone extinction, CRM remained intact though somewhat reduced in amplitude and area. Alternatively, when CRM was successfully extinguished via US-alone presentations, CRs remained intact. Meanwhile, unpaired extinction, which involved presentations of both the CS and US, was observed to most successfully extinguish both CRs and CRM.

If CRM is a generalized CR, a US modality that supports a high level of NMR conditioning should also elicit strong CRM. However, it was found that although both a 2-mA ES and a moderately intense 4-PSI air puff (AP) supported similar terminal levels of NMR conditioning, in excess of 90% following six days of pairings, only conditioning with the 2-mA ES resulted in strong CRM (Buck, Seager, & Schreurs, 2001). However, robust CRM was observed when a more intense, and presumably, more aversive, 8-PSI AP was employed during NMR conditioning.

If CRM is a generalized CR, we could expect to see the strongest CRM in subjects that are most strongly conditioned. Our lab has found that 99% of research subjects become highly conditioned (> 80% CR) to the tone CS but high levels of NMR conditioning do not necessarily ensure strong CRM. In fact, only approximately 25% of our subjects show strong CRM with the remaining subjects showing moderate levels, low levels or even no CRM (Smith-Bell, Burhans, & Schreurs, 2012). When correlations were examined between CR dependent variables (e.g., frequency, onset latency, and area under the response curve) and level of CRM, the strongest predictors of CRM, as indexed by an increase in percent change in the magnitude of the area of the UR when examined following six sessions of NMR conditioning, were CR onset latency and CR area. Those rabbits whose CRs began more immediately after the onset of the CS and those rabbits with larger CR areas were more likely to exhibit strong CRM than other subjects.

Previous CRM experiments reported NMR conditioning data averaged across all rabbits receiving paired NMR conditioning (Burhans, Smith-Bell, & Schreurs, 2015; Schreurs et al., 1995, 2000). However, averaging group NMR conditioning data is known to mask behavioral phenomena and group averages may suggest that all subjects learn at the same rate in a monotonically increasing fashion (Gallistel, Fairhurst, & Balsam, 2004; Halverson, Hoffmann, Kim, Kish, & Mauk, 2016). By dividing subjects into groups based on the time point in a session when a specific learning criterion was met, Halverson et al. (2016) found systematic differences in the rate of conditioning and in CR amplitude.

Within-experiment variations in the levels of rabbit NMR conditioning may have an anatomical explanation. Using trace conditioning, Woodruff-Pak, Lehr, Li, and Liu-Chen (2010) reported higher levels of binding of $\alpha\beta$ heteromeric nicotinic acetylcholine receptors in the hippocampus of both young and old rabbits who were designated “good learners” rather than “poor learners” of a difficult trace conditioning task. Van der Zee, Kronforst-Collins, Maizels, Hunzicker-Dunn, and Disterhoft (1997) found significant differences between the level of protein kinase C- γ immunoreactivity in the hippocampus of trace conditioned rabbits designated “good learners” versus “slow learners.”

Anatomical differences in the cerebellum could influence variability in NMR acquisition during delay conditioning as well. Differences in learning-related synapse formation could play a factor. Kleim et al. (2002) reported that rats undergoing eyeblink conditioning had more excitatory synapses per interpositus nucleus neuron than unpaired or naïve controls. Age-related Purkinje cell loss and consequent decreases in cerebellar volume have been linked to compromised performance on delay eyeblink conditioning tasks in C57BL/6 mice aged 9–12 months (Vogel, Ewers, Ross, Gould, & Woodruff-Pak, 2002), and controlling for age-related hearing loss, Woodruff-Pak (2006) found a marginally significant inverse relationship between Purkinje cell counts and trials to criterion on a delay eyeblink conditioning task in C57BL/6 mice aged 4, 8 and 12 months. Schreurs, Gusev, Tomsic, Alkon, and Shi (1998) noted a strong relationship between cerebellar lobule HVI Purkinje cell dendritic excitability and % CR following one day of paired delay NMR conditioning in rabbits.

Taking into consideration that overall acquisition averages may be masking individual or group differences in CR and UR dependent variables, we separated subject data into five groups based on when they met a specific learning criterion (Halverson et al., 2016). Of particular interest was whether grouping subjects by CR data would consequently result in grouping subjects by strength of CRM. Because we have found that only a small subset of subjects show strong levels of CRM, we hoped to delineate aspects of NMR conditioning that could better clarify the relationship between NMR conditioning and CRM strength and to add to the debate of whether CRM is a CR that has generalized from the CS to the US.

2. Materials and methods

2.1. Subjects

Data were analyzed from 145 rabbits that were classically conditioned using our standard NMR delay conditioning paradigm. The data came from 34 rabbits in a published study (Burhans et al., 2015) and from 111 rabbits in four unpublished studies collected over a period of several years. Subjects were male, New Zealand White rabbits (*Oryctolagus cuniculus*), supplied by Harlan (Indianapolis, IN, USA) or Charles River (Saint Constant, Quebec, Canada) weighing 2.0–2.2 kg and aged 69–77 days upon arrival. Rabbits were housed in individual cages, given free access to food and water, and kept on a 12-h light/dark cycle. Upon arrival, rabbits were acclimated to housing conditions for one week prior to any behavioral manipulations and maintained in accordance with National Institutes of Health guidelines. The research was approved by the West Virginia University Animal Care and Use Committee.

2.2. Apparatus

The apparatus, data collection and analysis procedures for NMR conditioning have been described in detail previously (Schreurs, Smith-Bell, & Burhans, 2011b) and were modeled after those described by Gormezano (Coleman & Gormezano, 1971). During each behavioral session, each rabbit was placed in a natural sitting position in an adjustable Plexiglas box with ears restrained between layers of foam

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