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Inside the Thompson laboratory during the "cerebellar years" and the continuing cerebellar story

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ABSTRACT

This paper is based on the talk by one of the authors (DL) given at the symposium for the retirement of RF Thompson (RF Thompson: A bridge between 20th and 21st century neuroscience). We first make some informal observations of the historical times and research conditions in the Thompson laboratory when the cerebellum was found to play a critical role in eye lid classical conditioning, the "cerebellar years". These conditions influenced our collaborative international program on the phenomenon known as "transfer of training" or "savings". Our research shows that the appearance of "savings" is an artifact of the order of testing, and depends upon the functioning of the contralateral interpositus nucleus (IPN) in a way that is complementary to the role of the IPN in normal eyelid classical conditioning.

In this paper we first reflect on some of our experiences in Richard Thompson's laboratory during the time of the discovery of the cerebellar engram. We refer to these years (about 1980 to present) as "the cerebellar years" in contrast to the "hippocampal years" of the preceding decade. We then continue with one of the lasting effects of his research on the localization of eye blink classical conditioning to the cerebellum. We begin with some observations on the times and Thompson laboratory.

First, Dick moves a lot. I (DL) began a postdoc with Dick at UC Irvine in the summer of 1980 after I had spent an interim year of teaching at UC Riverside. It was a short stay at Irvine because Dick was about to move to Stanford University. In fact, Dick had a reputation for moving frequently, and this move would further support that reputation. My graduate mentors warned me of Dick's propensity for moving, and at his bad judgment of leaving the Lashley chair at Harvard University to return to Irvine. Being a (northern) Californian, however, I fully agreed with Dick's return to (southern) California, and my view was that Dick's bad judgment was in moving to Harvard in the first place. The short stay at Irvine was not entirely a surprise as Dick communicated with me his plans shortly before I was to begin my postdoc.

As Larry Swanson documented in the preceding talk, Dick moved from Oregon to Irvine to Harvard then back to Irvine to Stanford to USC. I would add a second move at USC. Dick moved twice to USC, first to the 10th floor of the Seeley G. Mudd building, and second to the 5th floor of the newly completed Hedco Neuroscience building. This may seem a trivial point, but it is not trivial to his students who had to dismantle, move, reassemble and calibrate the laboratory into working order, while tolerating the accompanying down time in their experiments.

Second, Dick's lab was big. It was filled with undergraduates, graduate students and postdocs. It is an apprentice model, where new people learned by joining experiments of more experienced persons, rank not withstanding. Dick has always welcomed undergraduates into his laboratory and afforded them unequalled opportunities to do cutting edge research, as Terry Milner noted in her talk. The graduate students were top-notch, being skilled, talented and hard-working. This was my first experience being around postdocs, myself being a new postdoc. Postdocs were a major source of a diverse range of research experience and expertise. The large number of students resulted in collaborative and helping spirits, inspiring a stimulating intellectual environment within the lab that in smaller labs takes extraordinary effort. Here it was the natural state of being.

As with any large group, there were cliques and friends who hung out together, a few solitary workers, and a few conflicts. Generally speaking, the conflicts were few and far between, and mostly resolved by avoidance, working with different testing equipment and at different times of day. Occasionally, Dick intervened by moving workers around, and his wife Judith was a stabilizing force in the later years. I never heard Dick yell at a student. He did occasionally yell at a secretary, but Dick was back to normal a short time later. The conflict was not personal, or taken personally by his experienced secretaries ("that's just Dick"), as it typically related to correcting wording in papers or grants. It was

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passion, not anger. Generally speaking, Dick followed his own advice to treat subordinates with deference.

The consequential conflicts in the laboratory were over resources like surgery, training apparatus, perfusion, histology. Students used sign-up sheets for these facilities, which worked reasonably well, and meant that the laboratory was used at all hours of the day and night and on week ends. After a minimal assignment of spaces for rabbits, perhaps the best indicator of status in the Thompson laboratory was the number of rabbit cages assigned to a student, animal space being the rate-limiting step to doing experiments. A student could increase the number of animals by collaborating with another student's projects.

Third, competition in publications was a clear feature in the Thompson laboratory. This competition took two forms. One form involved publishing before the competition, resulting in some studies being published in less prestigious journals, often with small N, or with results being published first in reviews. I know of one instance where a student did not publish an independent research paper because the student felt the results already had been published in a review, so why bother? As for the cerebellar story, we were confident of our results because we were our own worst critics, the results were robust, and different researchers within the lab independently replicated the results many times over (Clark, McCormick, Lavond, & Thompson, 1984; Lavond, Hembree, & Thompson, 1985; McCormick & Thompson, 1984). Robustness and independent replication are the important characteristics of science. None of our replications were purely replications, but rather were replications in the effort of further issues. Our research was inspired by our own thoughts, but the second form of competition involved addressing critics like John Welsh and John Harvey, and competitors in the cerebellar story like Chris Yeo. For myself, confronting the critics at meetings was the most unpleasant aspect of science and about the Thompson lab.

Fourth, there have been dramatic changes in technology that has impacted the Thompson laboratory over the years. This observation was not a part of my original talk due to time constraints and self-editing, but it is worth noting these changes here. At the time I entered the Thompson laboratory, the IBM Selectric typewriter was still the dominant piece of equipment in the office environment. All papers and grants were typed. At Stanford, the secretary upgraded to a dedicated word processor, then later to IBM personal computers. To the present time Dick continues to write in long hand on yellow legal pads though Dick was once a touch typist. The secretaries get good at deciphering Dick's scrawls, though occasionally I was asked to interpret one of Dick's impressions, usually turning out to be a technical term or a technical thought.

In the Thompson laboratory, each running chamber could be chronologically dated by the sophistication of the electronics at the time it was constructed or updated, ranging from Colbourne solid state units triggered by a relay that fell though a hole punched in a loop made from an old movie (it appeared to be a scene of a convertible driving along the French Riviera coast with Cary Grant and Grace Kelly in "To Catch a Thief") to achieve a variable interval between trials, to a custom programmed ROM for delay versus trace conditioning created at Irvine. At Irvine and the early days at Stanford all data was recorded on polygraphs and four channel reel-to-reel tapes to be played back to a PDP 12 computer (later sold for scrap) or the newer PDP 11 computer. (The out-of-order numbering is said to have to do with internal PDP machinations.) Years later we observed the impermanence of tapes as a method for preserving data as the recording media rubbed off on our hands. There were boxes and boxes of polygraph recordings. All this was eventually thrown out primarily due to lack of storage space. Scientists would keep everything if we could, no matter its value.

At Stanford the laboratory upgraded to personal computers to run the classical conditioning experiments, influenced in large part by postdoc Joe Steinmetz who was a recent graduate student in Mike Patterson's lab (which in turn was influenced by Dory Gormezano's FIRST system for the Apple II computer), scrapping the need for polygraphs and tape recorders. We began with an Apple II with runtime software (online experiment control, data collection and analysis) written in FORTH and assembly language for use with our own interface (written and designed by Lavond), and summary software for further off-line analysis was written in FORTH by Steinmetz. Being told by a visiting professor that Apples were "toys" not used by "real scientists", and possibly influenced by visiting professor Diana Woodruff-Pak who used an IBM PC for her writings, Dick shortly thereafter introduced the IBM Personal Computer to his secretary and to the lab, requiring a new interface and porting the FORTH and assembly software to the new platform. This system remained the dominant controller for conditioning experiments into the USC years, significantly improving the efficiency of the lab's experiments.

Fifth, Dick attracted a number of visiting professors from the States (for example, Paul Shinkman, Merle Prim, Diana Woodruff-Pak) and internationally (for example, Matti Mintz from Israel, and Tapani Korhonen and Markku Penttonen from Finland) to name a few I knew. I benefited in gaining international experience when Dick turned down their reciprocal invitations. I only wish Dick had a visiting professor from Spain, where it would be much easier for me to learn the language. On two trips before and after the first Gulf War, for a total of 15 weeks, I worked with Matti Mintz on classical conditioning of anesthetized rats. Here I learned two things: learning occurs to the extent that anesthesia is incomplete, and what it was like to be illiterate in a country where signs were in Hebrew and Arabic and few people outside universities or tourist areas spoke English. My more recent international experience has been five trips to Finland, for a cumulative total of 1 year, where I can at least read the signs and many people speak English, first with Tapani Korhonen and recently with Jan Wikgren and their students. This association with my colleagues in Finland is the subject of the experimental program discussed here.

The underlying theme of our research program is the discovery in the Thompson laboratory of the fundamental and essential role of the cerebellum in somatic classical conditioning. This discovery is the first time in history that a particular instance of learning has been localized to a small amount of critical tissue in the mammalian nervous system and is supported by about 30 years of study by Thompson and his associates (the "cerebellar years") into the phenomenon and alternative explanations. The one alternative explanation that escaped everyone's attention, even our own, is the phenomenon of "transfer of training" where it has long been observed that learning is unusually fast on the side opposite an interpositus lesion. The phenomenon of "transfer of training" seems to contradict the idea that an interpositus lesion selectively destroys the memory for classical conditioning. We have been following this implication in a research program over a number of years. The following discusses the issues and our research.

We begin with background observations setting up the problem. The results of Lavond et al. (1985) illustrate the issue. This is one of many retention studies that show normal training followed by a lesion of the cerebellar IPN on the trained side (here with kainic acid lesion) leading to a failure to retrain the lesioned side, and success at training the unlesioned side. From results like this we conclude that the cerebellum is essential for retention of the learned eye blink response. Little noticed is that the training on the unlesioned side is unusually fast. It is said that "savings" occurs, or that training has been "transferred" from the lesioned to the unlesioned side. The problem is that "savings" indicates that the memory still exists, that the memory has not been destroyed