INVESTIGATIVE REPORT

Monkey See, Monkey Do: Contagious Itch in Nonhuman Primates

Ashley N. FENERAN¹, Russell O'DONNELL², Ashley PRESS², Gil YOSIPOVITCH^{1,3,4}, Mark CLINE², Greg DUGAN², Alexandru D.P. PAPOIU¹, Leigh A. NATTKEMPER^{1,3}, Yiong Huak CHAN⁵ and Carol A. SHIVELY²

Departments of ¹Dermatology, ²Pathology/Comparative Medicine, ³Neurobiology & Anatomy, and ⁴Regenerative Medicine, Wake Forest School of Medicine, Winston-Salem, USA, and ⁵Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Clinical Research Centre, Singapore, Singapore

"Contagious itch" has been anecdotally reported and recently confirmed in a controlled setting in humans. Here, we investigated in adult rhesus macaques whether 'contagious itch' occurs spontaneously in monkeys. In a first experiment, the latency to scratch following cagemate scratching was observed in pair-housed adult rhesus macaques. Scratching increased within the first 60 s and subsequently declined. In a second experiment, scratching behavior was recorded for individually caged adult rhesus macaques which where shown videos of monkeys scratching, but also neutral stimuli. A greater frequency of scratching was observed when monkeys viewed a video sequence of another monkey scratching as well as during the neutral stimulus immediately following the monkey scratching segment. In conclusion, viewing other monkeys scratching significantly increased scratching behavior in adult rhesus macaques. Key words: contagious; scratching; itch; macaque; video; model; pruritus.

(Accepted April 17, 2012.)

Acta Derm Venereol 2013; 93: 27-29.

Carol A. Shively, PhD, Department of Pathology/Comparative Medicine, Wake Forest School of Medicine. Medical Center Boulevard, Winston-Salem, NC 27157-1071, USA. E-mail: cshively@wakehealth.edu

Itch is an unpleasant sensation that all humans experience in the course of their lives (1). In addition to common itch, chronic itch is a common symptom among dermatologic patients with a significant impact on quality of life in patients of all ages (2). Itch is also a common problem in veterinary medicine, where it elicits the desire to scratch, chew and initiate other forms of self-trauma (3).

Everyday life experiences suggest that itch can be socially contagious or easily inducible by mental suggestion. Published reports support the view that this intriguing phenomenon manifests in human beings and is amplified in atopic dermatitis (4, 5). An animal model of contagious itch would be helpful to elucidate the underlying mechanism and could provide important clues for developing a novel therapeutic approach. In this study, we tested the hypothesis of itch being socially contagious in adult rhesus monkeys (*Macaca mulatta*). We chose this nonhuman primate because of its similarity in anatomy, physiology and particularly central nervous system (CNS) function to humans.

MATERIALS AND METHODS

The measurement of itch can be inferred from observation of scratching behavior, so therefore we recorded the number of scratching bouts as an indicator of itch (4, 5). To distinguish from touching events, scratching was operationally defined as moving the fingertips repeatedly across the same skin area for a duration longer than one second. The location of scratching was recorded and classified by anatomical region: head, ventral surface of the trunk (body), leg (right or left), arm (right or left), dorsal surface of the trunk (back). Procedures involving monkeys were conducted in accordance with state and federal laws, the standards of the Department of Health and Human Services and Institutional Animal Care and Use Committee guidelines.

Experiment 1. Subjects were 16 healthy, adult male rhesus macaques (*Macaca mulatta*) pair-housed for a minimum of 18 months with indoor and outdoor access, in pens measuring $2.4 \times 2.3 \times 2.4$ m, at the Wake Forest University Primate Center (WFUPC). Monkeys ranged from 5.5–8.3 years old (mean age 6.3 ± 0.8). All monkeys were fed the same diet of standard monkey chow.

Each pair was observed during 2 intervals of 20 min using a group focal observation method (6). All occurrences of scratching were recorded. The time intervals elapsed between one monkey scratching and its cagemate scratching were recorded. These elapsed times were used as the dependent variable (as the 'latency' to scratch following cagemate scratch). Each instance of scratching in one cagemate was considered the start point for the elapsed time until the other cagemate scratched in turn. All observations were made at approximately the same time each day over a span of 3 days. Observations were made by 2 observers, and interobserver reliability was greater than 0.92%.

Cumulative sum (CUSUM) analysis was performed to determine the point by point sequential trend in the time elapsed between one monkey responding to a scratching event in the other (latency to scratch) and also to document the shift in scratching-pattern over the observation period. CUSUM is the running total of differences between the individual data points and the mean of all data points (7). The total number of scratching episodes was averaged over the total number of time periods. CUSUM of the first time period was defined as the difference between the number of scratching episodes in that period and the mean scratching frequency of the total time. For the next time period, the CUSUM of the previous period was added to the difference between the number of scratching episodes in the new time period and the mean scratching frequency of the total time. This process was continued through the last time period. The trend was later analyzed using linear regression to assess its statistical significance (set at p < 0.05).

Experiment 2. Subjects were 10 adult male rhesus macaques housed in single cages that measured $1.7 \times 0.86 \times 0.76$ m. Subjects ranged from 6.5–15.2 years old (mean age 11.0 ± 3.3). All monkeys consumed standard monkey chow. Monkeys in

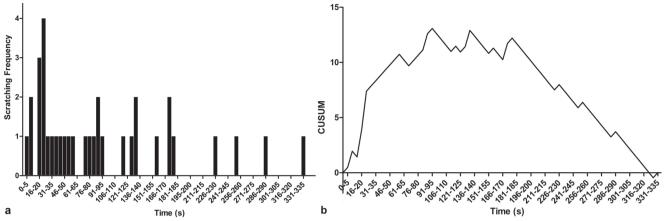


Fig. 1. Frequency distribution of latencies to scratch following cagemate scratch. Most scratching episodes occurred within the first 60 s following cagemate scratch and decreased thereafter (a). Cumulative sum (CUSUM) graph monitoring change in scratching occurrence over time. There is an increasing trend until the 56-60 s interval, indicating a contagious effect that then plateaus and decreases, indicating that the contagious effect gradually wears off (b).

experiment 2 did not participate in experiment 1 and were unfamiliar with experiment 1 monkeys.

A video was created using monkeys from experiment 1. Video segments contained a monkey scratching a part of his body but did not contain his face to prevent eliciting a fear or aggression response in monkeys viewing the video. Monkeys in experiment 2 were shown this video for the first time and were unfamiliar with the contents of the video until it was revealed in this experiment.

The video consisted of 2 sequences. Each sequence was comprised of a series of 5 30-s segments. The segments were either 'Neutral" (a fruit), "Active" (a monkey scratching), or "Passive" (a monkey not scratching). To counterbalance order of presentation, Active and Passive segments were alternated in the two sequences. The order of the 5 segments in the first sequence was: Neutral, Active, Neutral, Passive, Neutral; and the order in the second sequence was: Neutral, Passive, Neutral, Active, Neutral. Each animal viewed both sequences in the same order. All instances of scratching during the video were recorded. In order to capture contagious scratching events occurring in the follow-up Neutral segments, scratching episodes that occurred during the Active segment plus the Neutral segment immediately following were summed (60 s total). Likewise, scratching episodes that occurred during the Passive segment plus the Neutral segment immediately following were summed (60 s total). A Wilcoxon signed rank test was performed to determine whether scratching behaviors differed between these two 60 s periods.

RESULTS

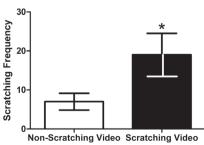
Experiment 1. Fourteen of the 16 monkeys exhibited scratching following cagemate's scratch within 360 s of its cagemate scratching. A total of 35 scratching episodes were recorded (Fig. 1a). Seventeen scratching episodes were recorded within the first 60 s following a cagemate's scratch. The remaining 18 scratching episodes occurred between 61–360 s afterwards.

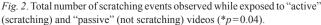
CUSUM analysis revealed a significant increasing trend [p < 0.001, rate of scratching was 0.983 (95% CI 0.785–1.182)] of scratching episodes until the time period of 56–60 s (Fig. 1b). From 56–60 s to 176–180 s, the trend reached a plateau [p = 0.374, rate of scratching was 0.025 (95% CI –0.032–0.081)] and decreased for the remainder of the 300 s [p < 0.001, rate of scratching

was -0.386 (95% CI -0.4 to -0.372)]. An analysis of the location of the scratching responses indicated that 29% were directed at the same location as in the originating (inducer) monkey, while 71% targeted different areas. *Experiment 2*. During the Active plus following Neutral segment, 19 total scratching events occurred (median=1.5 per monkey). During the Passive plus following Neutral segment, monkeys scratched 7 times (median=0.0) (p=0.04) (Fig. 2). Three monkeys did not scratch during any portion of the experiment.

DISCUSSION

In its basic, most primitive form, scratching has been historically considered a reflex controlled by the spinal cord that required no input from the brain (8). However, scratching is clearly more than a spinal reflex since it depends on a top-down strategy for scratching to be effective at relieving itch and also involves hedonic aspects (9). Our group previously demonstrated that exposure to images suggestive of itch have the intriguing effect of inducing itch and scratching. This visually transmitted phenomenon was amplified in patients with atopic dermatitis, who thus appeared more suggestible to visual cues of itch (5). Another study demonstrated that contagious scratching was induced in a public lecture on itch (4). This behavioral response could involve mirror neurons, which are activated when one individual either performs an action





or observes another individual performing an action (10, 11). Another experiment used unfamiliar monkeys and observed their response to conspecific scratching (12). When one target monkey watched an unfamiliar monkey through a peephole, there was increased probability that an observer monkey would scratch after watching the target monkey perform scratching behavior. This study made important observations on the contagion of itch in monkeys. However, the study sample was small (n=5) and utilized a constructed experimental model that may have enhanced arousal in the monkeys, thus leading to exaggerated outcomes as scratching became a way to cope with negative arousal.

In the present study, we confirm that when monkeys view other monkeys scratching they significantly increase scratching behavior. In the first experiment, it was evident that when one monkey started scratching their cagemate scratched shortly thereafter.

The target site of contagious scratching movements was in 71% of cases different from the site spontaneously scratched by the first monkey, supporting a previous observation in humans that contagious itch induced primarily by visual cues exhibits a widespread distribution, in other words it is not location-specific (5). This feature could very well constitute a hallmark of the "contagious itch" phenomenon, and be directly (and mechanistically) derived from its initiation in the superior structures of CNS, and not in the periphery. Secondly, this feature also suggests that contagious itch is not simply a mimicking behavior.

This "contagious" itch could represent an empathic type of response. In the second experiment, individually housed monkeys responded to videos of stranger (unfamiliar) monkeys actively scratching, but not to a passive monkey (not scratching), or to neutral images. Significantly more scratching episodes were observed during the active scratching video segments and immediately following them, likely owing to a lag time between the initial stimulus and the monkey 'catching' an itch, and not due to neutral stimulus.

Contagious yawning is another well-documented behavior, and approximately 45-60% of the human population is susceptible to this phenomenon (13). It is thought to be related to empathic capacity. Infants and young children do not catch a yawn when exposed to either family members or unfamiliar individuals who are yawning (14). Contagious yawning can be transmitted horizontally within representatives of the same species (humans, Gelada baboons) and vertically, from one species to another (from humans to dogs) (13, 15, 16). The results of studies in chimpanzees and stumptail macaques demonstrated that nonhuman primates shown a video of conspecifics yawning, yawn as well. As with contagious yawning, it is suggested that contagious scratching arises from tension of viewing an outgroup monkey (17). In our experiment, we excluded adult male monkey faces to minimize a tension or aggression response that could result in scratching. Thus, our results are more likely to reveal a contagious behavior and are less likely to represent a response resulting simply from viewing an outgroup monkey. This study confirms the hypothesis that itch is socially contagious in nonhuman primates. Further investigation of the neurophysiological mechanisms underlying this behavioral response could identify the relays involved within the CNS and potentially lead to more effective treatments for itch.

ACKNOWLEDGMENTS

Dr. Cline provided the animals studied, which are in a long-term observational cohort supported by NIAID U19 AI67798. Dr. Yo-sipovitch is supported by grant NIH R01 55902-3. Dr. Shively is supported by NIH R01 HL087103 and NIH R21 MH086731.

REFERENCES

- Yosipovitch G, Greaves MW, Fleischer AB, McGlone F. Itch: Basic Mechanisms and Therapy. New York: Marcel Dekker, 2004.
- 2. Yosipovitch G, Greaves MW, Schmelz M. Itch. Lancet 2003; 361: 690–694.
- Olivry T, DeBoer DJ, Favrot C, Jackson HA, Mueller RS, Nuttall T, et al. Treatment of canine atopic dermatitis: 2010 clinical practice guidelines from the International Task Force on Canine Atopic Dermatitis. Vet Dermatol 2010; 21: 233–248.
- Niemeier V, Kupfer J, Gieler U. Observations during itchinducing lecture. Dermatol Psychosom 2000; 1: 15–18.
- Papoiu AD, Wang H, Coghill RC, Chan YH, Yosipovitch G. Contagious itch in humans: a study of visual 'transmission' of itch in atopic dermatitis and healthy subjects. Br J Dermatol 2011; 164: 1299–1303.
- Altmann, J. Observational study of behavior: sampling methods. Behaviour 1974; 48: 227–267.
- Grigg OA, Farewell VT, Spiegelhalter DJ. Use of risk-adjusted CUSUM and RSPRT charts for monitoring in medical contexts. Stat Methods Med Res 2003; 12: 147–170.
- Sherrington CS. Observations on the scratch-reflex in the spinal dog. J Physiol 1906; 34: 1–50.
- 9. Yosipovitch G, Ishiuji Y, Patel TS, Hicks MI, Oshiro Y, Kraft RA, et al. The brain processing of scratching. J Invest Dermatol 2008; 128: 1806–1811.
- Wood JN, Glynn DD, Hauser MD. Rhesus monkeys' understanding of actions and goals. Soc Neurosci 2008; 3: 60–68.
- Iacoboni M, Dapretto M. The mirror neuron system and the consequences of its dysfunction. Nat Rev Neurosci 2006; 7: 942–951.
- Nakayama K. Observing conspecifics scratching induces a contagion of scratching in Japanese monkeys (Macaca fuscata). J Comp Psychol 2004; 118: 20–24.
- Senju A. Developmental and comparative perspectives of contagious yawning. Front Neurol Neurosci 2010; 28: 113–119.
- Millen A, Anderson JR. Neither infants nor toddlers catch yawns from their mothers. Biol Lett 2011; 7: 440–442.
- 15. Joly-Mascheroni RM, Senju A, Shepherd AJ. Dogs catch human yawns. Biol Lett 2008; 4: 446–448.
- Palagi E, Leone A, Mancini G, Ferrari PF. Contagious yawning in gelada baboons as a possible expression of empathy. Proc Natl Acad Sci USA 2009; 106: 19262–19267.
- Paukner A, Anderson JR. Video-induced yawning in stumptail macaques (Macaca arctoides). Biol Lett 2006; 2: 36–38.