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Detectability and Appraisal Thresholds of Split Pulse Signals for the MemoPatch™ Device, an Electronic Skin Patch Intended to Deliver Tactile Medication Reminder Signals (Study TS-104)

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Abstract—**Patient non-adherence to prescribed medication regimens is a significant problem and affects clinical treatment outcomes. The MemoPatch™ medical device, currently in development, is an electronic skin patch intended to deliver tactile medication reminder signals. Fifty volunteers completed a laboratory experiment that evaluated the detectability and appraisal thresholds of five split signals; specifically, the current thresholds (in mA) at which a signal was detected (threshold T1), was considered sufficiently detectable to serve as a reminder signal (threshold T2), and became too strong as a reminder signal (threshold T3). Signals were selected under consideration of three data points: $T1_{Max}$ and $T2_{Max}$ (defined as, resp., the maximum current observed at T1 and T2) and $T3_{Pct90}$ (the T3 current at the 90th percentile). A signal was considered to be useable in future versions of the MemoPatch™ device if it met the constraint that (T3Pct90−T2Max) should not be negative. One signal met the constraint requirement as its T3Pct90−T2Max=0.96mA.**

Keywords: adherence; pulse signals; detectability; patch

I. Introduction

Patient adherence refers to "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [1]. A quantitative review put the prevalence of non-adherence to medication regimens across 17 disease conditions at 24.8% [2]. In one survey, unintended forgetfulness was cited by 64.4% of respondents as the main reason for non-adherence [3].

MemoPatch™, a device currently being developed, is an electronic skin patch intended to deliver discreet tactile reminder stimuli [4]. In its commercial versions, the MemoPatch™ device will consist of a thin flexible self-adhesive dermal patch with an integrated pulse generator application specific integrated circuit (ASIC), printed battery, body contact electrodes, and optionally a printed antenna enabling wireless programming. Significant energy savings could be achieved if the pulse were split with a separation of 5 milliseconds (ms) between the alternations.

The objective of the present study (TS-104) was to evaluate the functional detectability of five split signals derived from signals retained from earlier experiments [5].

II. Methods

A. Design and Sample

TS-104 was a standardized laboratory experiment in a sample of consenting sufficiently healthy adults. During a single experimental session, subjects were exposed to a fixed-order set of four training signals followed by a randomly ordered sequence of five split reminder signals.

Eligible were adult (age > 18 years) male and female healthy volunteers; as well as volunteers with illnesses that were being treated according to the prevailing standard of care, that did not impair subjects' ability to detect reminder signals, and that did not predispose them to potential adverse events. Exclusion criteria comprised several current, recent, or history of various dermatological, neurological, psychiatric, and cardiovascular diseases; diabetes with end-organ damage; transplantation; topical medication and other treatments, including anesthetics, applied to upper arm; and pregnancy or potential pregnancy. Subjects were recruited from a registry of volunteers enrolled independently from the student, faculty, and staff bodies of Hasselt University (Diepenbeek, Belgium).

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B. Signals

The five reminder signals examined in this study consisted of split pulses where the alternations are separated by 5 ms; combined with fixed pulse intervals into bursts of a fixed length; in turn combined with fixed burst intervals into a reminder signal. Each signal was tested with a compliance voltage of 70V and initiated with an electric current of 0 mA. The current was increased gradually over the course of the experiment. Subjects were asked to indicate three transition points: when a signal was detected (T1), when the signal was sufficiently detectable to serve as a reminder signal (T2), and when that signal became too strong as a reminder signal (T3). Current (in mA) was recorded for each subject at T1, T2, and T3 and constituted the subject's threshold currents for each transition.

C. Experimental Test Configuration and Procedures

As shown in Fig. 1, pulses were generated by an Arbstudio 1102 arbitrary waveform generator (LeCroy, Chestnut Ridge, NY, USA) [A] based on parameters specified by the program Arbstudio v.3.2.0.2 (LeCroy, Chestnut Ridge, NY, USA) running on a personal computer (Dell, Precision M6600, Round Rock, TX, USA) under the Microsoft Windows 7 operating system (Microsoft, Redmond, WA, USA) [B]. Pulses thus generated were amplified by a custom-designed output stage (manufactured by Dekimo, Gentbrugge, Belgium) [C] and transmitted to the FCB patches [F]. An oscilloscope (Tektronix, TPS2024B, Beaverton, OR, USA) was used to measure voltage and current [D]. To prevent leak currents from interfering with equipment, the connection of each of the devices [A], [B], [C], and [D] to the electrical grid was regulated by a medical device certified power supply meeting the IEC 60601-1 international standard [E]. A 5x5 cm wired patch with a flexible circuit board [F] was affixed to subjects' upper arm of choice. This experimental patch had two leads of approximately 10cm with rigid ending to fit into a zero insertion force (ZIF) connector on the output stage.

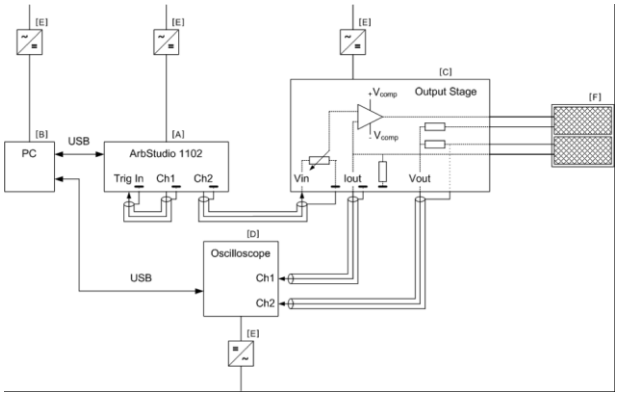

Figure 1. Experimental test configuration.

After completing eligibility verification and obtaining written informed consent, subjects' demographics, relevant anthropo- and biometrics, relevant medical history and current clinical status were recorded. Body mass index (BMI) was calculated as the subject's weight (in kilogram) divided by the square of his/her height (in meter) without corrections. Upper arm circumference was assessed (in cm) at the mid-point between the tip of the shoulder and the tip of the elbow by means of a tape measure. Pilodensity on the upper arm was determined by means of the Modified Ferriman-Gallwey score, a visual scale by which observed hair concentration is matched to one of four grades of density [6]. Upper body adiposity, expressed as % body fat, was evaluated with the Omron Body Fat Monitor BF306 (Omron Healthcare Co., Ltd., Kyoto, Japan).

Subsequently, a training sequence of four signals was administered in fixed order to train subjects in the study procedures. Next, the five experimental signals were administered in random order. To avoid an alertness effect, subjects were not told that the first four signals were for training purposes. Each signal was administered in a separate signal event. Subjects were instructed to raise a hand if and when a signal was detected (T1), when the signal was sufficiently detectable to serve as a reminder signal (T2), and when that signal became too strong as a reminder signal (T3). The corresponding currents were recorded. Following each signal event, subjects were asked to report any untoward events. Following completion of the signal sequence, the patch site was examined to observe for any adverse events. Subjects were debriefed, including information as to how to contact the investigators in case of adverse events occurring after the study visit.

III. Results

A. Subjects

Fifty subjects, 28 female (56.0%) and 22 (44.0%) male (p=ns) and all caucasian, completed the experiment. Table 1 summarizes relevant demographics, anthropo- and biometrics for the sample and stratified by gender. The mean age ($\pm$SD) was 41.9$\pm$15.4 with no statistically significant difference for gender. Men and women differed significantly in mean weight, height, and upper body adiposity (all $p<0.001$) but not BMI and upper arm circumference (both p=ns). This was confirmed in contingency analyses of gender by categories of age, BMI, and upper arm circumference (all p=ns) and upper body adiposity (p=0.001). Note that all women had a pilodensity rating of 1 compared to 86.4% of men, among whom the remaining 13.6% had a rating of 2. Hence, and even though these differences were marginally statistically significant (p=0.044), no further analyses stratified by pilodensity were performed, as they would revert back to stratification by gender.

B. Detectability and Acceptability Thresholds of Test Signals

Table 2 lists, for each pulse, the central tendency and dispersion statistics for the currents observed at T1, T2, and T3. Comparative analyses revealed statistically significant gender differences in the currents recorded at T1 and T2 for signals P–01 (p_{T1}=0.002, p_{T2}=0.016), P–02 (p_{T1}=0.001,

p_{T2}=0.011), P–03 (p_{T1}=<0.001, p_{T2}=0.027), P–04 (p_{T1}=<0.001, p_{T2}=0.007), and P–05 (p_{T1}=0.004, p_{T2}=0.021), with mean thresholds for women being consistently lower than those for men. For signal P–02, the T3 mean threshold was significantly lower for women than for men (p=0.038). There were no statistically significant differences by gender on the mean T3 threshold currents for the remaining four signals though a marginal trend could be detected (all four p≥0.050, but ranging from 0.050 to 0.092).

In bivariate analyses, correlation coefficients between subjects' current thresholds and, respectively, upper arm circumference (all p=ns) and BMI (all p=ns) were statistically not significant across all signals and all transition points. Significant negative correlation coefficients were observed between subjects' current thresholds and upper body adiposity. Including all three transition points, for signal P–01 the correlation coefficients were –0.445 (p_{T1}=0.001), –0.448 (p_{T2}=0.001), and –0.483 (p_{T3}=<0.001); for signal P–02, –0.500 (p_{T1}=<0.001), –0.502 (p_{T2}=0.001), and –0.491 (p_{T3}=<0.001); for signal P–03, –0.454 (p_{T1}=0.001), –0.416 (p_{T2}=0.003), and –0.459 (p_{T3}=0.001); for signal P–04, –0.411 (p_{T1}=0.003), –0.391 (p_{T2}=0.005), and –0.471 (p_{T3}=0.001); and for signal P–05, –0.418 (p_{T1}=0.003), –0.458 (p_{T2}=0.001), and –0.528 (p_{T3}=<0.001). Thus the percentage variance in subjects' threshold currents accounted for by upper body adiposity ranged from 15.3% to 27.9%.

Multiple linear regressions were performed to model subjects' current thresholds at each transition point as a function of age, male gender, upper arm circumference, BMI, and upper body adiposity. These analyses confirmed that currents recorded were a function of adiposity for thresholds T2 and T3 (p-values ranging from 0.019 to 0.001) but not threshold 1 (all p=ns); not a function of arm circumference (all p=ns) and BMI (all p=ns); and neither a function of age (all p=ns) or gender (all p=ns).

C. Signal Selection

Referring to Table 2, three data points are important in terms of identifying a pulse current that could be used in future testing and commercial versions of the MemoPatch™ device:

- $T1_{Max}$: maximum (Max) current observed at T1. This refers to the 50th highest T1 threshold observed for a given signal in this study's sample; i.e., pulse currents less than or equal to this value were observed by all subjects. This data point validates that all subjects detected the signal.
- $T2_{Max}$: maximum (Max) current observed at T2. This denotes the 50th highest T2 threshold observed for a given signal in this study's sample. Provided that a signal's pulse current ≥ $T1_{Max}$, signals with pulse currents ≤ $T2_{Max}$ were observed by all subjects.
- $T3_{Pct90}$: the T3 current at which 90% of the sample considered a signal to transition to being too strong. One could argue that $T3_{max}$ should be used to assure inclusion of all subjects, however it is known that the distribution of humans' tolerance for currents is skewed and that some require very high currents before experiencing discomfort. The choice of the 90th percentile is to avoid signals with currents that would be discomforting to a significant group of users and is a constraint imposed on $T2_{Max}$.

Therefore, for a signal to be useable in future versions of the MemoPatch™ device, the difference between $T3_{Pct90}$ and $T2_{Max}$ should not be negative; or ($T3_{Pct90}$–$T2_{Max}$) ≥ 0. Table 3 reviews each signal in terms $T1_{Max}$, $T2_{Max}$, $T3_{Pct90}$, and ($T3_{Pct90}$–$T2_{Max}$). Signal P–01 had $T3_{Pct90}$–$T2_{Max}$ = 0.96 mA and therefore met the constraint requirement. The four other signals all had $T3_{Pct90}$<$T2_{Max}$ and therefore failed the constraint requirement.

IV. COMMENT

The MemoPatch™ device aims to enhance adherence to medication treatment regimens by reducing unintended forgetfulness, the most common cause why patients fail to take their medications as prescribed. The signals generated should be perceptible enough yet without producing discomfort and pain. This fourth in a series of signal-finding studies evaluated five signals with split pulses and identified one that met requirements.

Subjects detected signal P–01 at currents ranging from 5.6 to 19.2 mA (T1); considered the signal sufficiently strong to serve as a reminder signal at currents between 7.2 and 26.0 mA (T2); and rated the signal as too strong at currents from 8.4 to 37.2 mA (T3). With the 90th percentile for T3 at 26.96 mA, signal P-01 offers a reminder signal that includes the $T2_{Max}$ current of 26.0 mA.

The current at transition T3 is the point at which subjects stated that the current was becoming too strong. One could argue that therefore the highest allowable current should be less than the T3 threshold current. Strictly, this would be correct, was it not that the laboratory context was a static situation: all subjects were seated; informed to expect signals and therefore alert if not vigilant; and focused on the experiment. In contrast, future users of the MemoPatch™ will be wearing the patch under dynamic conditions of arousal and activity. What might be considered "too strong" in the laboratory is hypothesized to be "appropriate" in day-to-day situations. This is being tested in study TS–201, another pre-patient study in which sufficiently healthy volunteers similar to those in this study will be asked to apply and wear a printed circuit board patch for two days and execute an action (in this case, sending a mobile phone text message) in response to a signal activation.

In this present study, upper body adiposity was inversely related to current: as adiposity increased, T1, T2, and T3 current thresholds decreased. Adiposity is known to correlate with impedance [7], which in turn, per Ohm's law, is correlated negatively with current. Whether gender played a role in the appraisal of currents is unclear. In multivariate analyses that also included other possible determinants of perceived current thresholds, gender was not a significant variable across signals and, within each signal, across transition points T1, T2, and T3.

TABLE 1. SAMPLE CHARACTERISTICS

	All subjects (n=50)					Female n=28 (56.0%)					Male n=22 (44.0%)					*P*
	Min	*Max*	*M*	±	*SD*	*Min*	*Max*	*M*	±	*SD*	*Min*	*Max*	*M*	±	*SD*	
Age (years)	18	68	41.9	±	15.4	18	67	43.0	±	15.1	21	68	40.5	±	16.1	ns
Weight (kg)	48	111	72.9	±	14.0	48	94	67.0	±	11.6	59	111	80.4	±	13.4	<0.001
Height (cm)	151	190	170.1	±	8.9	151	180	165.2	±	6.8	163	190	176.3	±	7.4	<0.001
BMI (kg/m^2)	17	39	25.2	±	4.5	17	35	24.6	±	4.5	19	39	25.9	±	4.5	ns
Upper arm circumference (cm)	21	34	28.7	±	3.3	21	34	28.1	±	3.3	23	34	29.4	±	3.1	ns
Upper body adiposity (% body	9	46	29.4	±	9.6	21	46	34.4	±	7.3	9	39	23.1	±	8.4	<0.001

TABLE 2. CURRENT (mA) FOR EACH PULSE AT EACH TRANSITION

Signal		Min	Max	Mean	95% CI	SD	Pct25	Pct50	Pct75	Pct90
P-01	T1	5.6	19.2	8.88	8.13 - 9.63	2.63	7.10	8.60	9.60	11.60
	T2	7.2	26.0	13.54	12.31 - 14.76	4.31	10.30	12.60	15.30	21.12
	T3	8.4	37.2	18.47	16.73 - 20.22	6.14	13.60	17.20	22.10	26.96
P-02	T1	6.4	21.6	10.22	9.41 - 11.04	2.85	8.80	9.60	11.20	14.36
	T2	8.8	37.6	16.00	14.35 - 17.65	5.80	12.80	14.40	17.80	23.76
	T3	10.4	42.4	21.48	19.51 - 23.45	6.94	16.30	20.80	25.30	29.08
P-03	T1	5.2	19.6	8.66	7.93 - 9.40	2.59	7.20	8.00	9.30	12.00
	T2	6.8	28.8	13.00	11.73 - 14.27	4.46	10.30	12.00	14.40	19.68
	T3	8.0	34.4	17.78	16.08 - 19.47	5.96	14.20	16.80	20.80	24.72
P-04	T1	6.0	20.0	9.94	9.15 - 10.74	2.79	8.30	9.40	10.50	13.60
	T2	8.4	31.2	15.32	14.00 - 16.64	4.66	12.00	14.20	17.20	23.16
	T3	9.2	41.2	21.43	19.47 - 23.39	6.89	16.60	20.20	26.10	29.96
P-05	T1	5.6	18.8	8.33	7.67 - 8.98	2.31	7.10	7.60	9.30	10.40
	T2	6.8	28.0	12.83	11.69 - 13.97	4.02	9.90	12.20	14.50	19.04
	T3	8.0	35.2	17.77	16.19 - 19.35	5.56	13.10	17.00	20.90	25.60

TABLE 3. ANALYSIS OF SIGNAL CURRENTS

Signal	$T1_{Max}$	$T2_{Max}$	$T3_{Pct90}$	$T3_{Pct90} - T2_{Max}$
P-01	19.2	26.0	26.96	0.96
P-02	21.6	37.6	29.08	-8.52
P-03	19.6	28.8	24.72	-4.08
P-04	20.0	31.2	29.96	-1.24
P-05	18.8	28.0	25.60	-2.40

The findings of this study contribute significantly to the development of an independent reminder device (including its own power source). The MemoPatch™ device aims to be a discrete (i.e., private), non-audible reminder technology perceptible exclusively, and this under all conditions, by the person wearing the device. This is in contrast to other non-audible reminder solutions such as vibrating phones of other mobile devices. However, these solutions require the person to remember taking the device along; and, depending on where the device is at the time of activation, may or may not be perceptible to others.

In summary, this study identified a signal (P–01) as effective and appropriate for use in future test and commercial versions of the MemoPatch™ device. Like the other signals, it was found to be (virtually) independent from age, BMI, upper arm circumference, and gender.

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