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Temporal Dynamics of Transdermal Alcohol Concentration Measured via New Generation

Wrist-Worn Biosensor

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32   Abstract

33   **Background:** The development of a transdermal alcohol biosensor could represent a tremendous

34   advance towards curbing problematic drinking. But several factors limit the usefulness of extant

35   transdermal technology, including relatively lengthy delays between blood alcohol concentration

36   (BAC) and transdermal alcohol concentration (TAC), as well as the large/bulky designs of

37   currently available transdermal sensors (e.g., ankle monitors). The current research examined the

38   lag time between BAC and TAC using a prototype of BACtrack Skyn—a new-generation wrist-

39   worn transdermal sensor featuring a compact design and smartphone integration. **Methods:**

40   Participants (N=30) received either a dose of alcohol (target BAC .08%) or a non-alcoholic

41   beverage in the laboratory while wearing both the AMS SCRAM ankle monitor and a Skyn

42   prototype. Participants were monitored in the laboratory until breath alcohol concentration

43   (BrAC) dropped below .025%. **Results:** Device failure rates for Skyn prototypes were relatively

44   high (18%-38%) compared with non-prototype SCRAM devices (2%). Among participants with

45   usable data, both Skyn and SCRAM-measured TAC showed strong correlations with BrAC, and

46   both Skyn and SCRAM devices detected alcohol within 30-minutes of first alcohol-

47   administration. Skyn-measured TAC peaked over 1-hour earlier than SCRAM-measured TAC

48   (54 versus 120 minutes after peak BrAC, respectively), and time-series models suggested that, on

49   average across all measured portions of the BrAC curve, Skyn-TAC lagged behind BrAC by 24

50   minutes, whereas SCRAM-TAC lagged behind BrAC by 69 minutes—all differences statistically

51   significant at $p<.001$. **Conclusions:** Results provide preliminary evidence for the validity of a

52   new-generation wrist-worn transdermal sensor under controlled laboratory conditions, and

53   further suggest favorable properties of this sensor as they pertain to the latency of transdermal

54   alcohol detection. The prototype-version of Skyn employed here displayed a higher failure rate

55   compared with SCRAM and, in future, more reliable and robust Skyn prototypes will be required

56   suitable to field testing across diverse environmental conditions.

57   *Keywords*: Alcohol, biosensor, transdermal, BAC, measurement

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62   The development of a wearable alcohol biosensor could represent a key advance toward

63   helping people make informed decisions about their drinking and, potentially, toward curbing

64   alcohol-related morbidity and mortality. Devices for the objective quantification of behaviors

65   have long been of interest to researchers and consumers across health domains (e.g., fitbit for

66   exercise; Haynes & Yoshioka, 2007), but, due to alcohol's neurocognitive effects and also

67   cultural conventions surrounding drinking, the need for a biosensor to measure alcohol

68   consumption has loomed particularly large. Specifically, drinking at more extreme levels is

69   associated with memory and cognitive disruptions that can impair awareness of the quantity of

70   alcohol consumed (Weissenborn & Duka, 2003; White, 2003). Further, standard drink sizes and

71   quantities can vary widely so that even the cognitively alert drinker may not always be aware of

72   the amount of alcohol she ingests (Barnett, Wei, & Czachowski, 2009; Kerr, Greenfield,

73   Tujague, & Brown, 2005; Kerr, Patterson, Koenen, & Greenfield, 2008). Finally, societal stigma

74   can accompany alcohol consumption for many individuals such that, even given an awareness of

75   their own drinking practices, some might be reluctant to share this information with others, thus

76   interfering with the identification of those in need of alcohol intervention as well as the

77   investigation of drinking behavior via research (Davis, Thake, & Vilhena, 2010; George,

78   Gournic, & McAfee, 1988; Zapolski, Pedersen, McCarthy, & Smith, 2014). A wearable alcohol

79   biosensor might serve health needs across a variety of domains, including aiding prevention of

80   alcohol-related disorders (Fairbairn & Kang, in press), improving outcomes in harm reduction

81   alcohol intervention programs (Barnett, 2015), reducing the number of alcohol-related motor

82   vehicle fatalities (Blincoe, Miller, Zaloshnja, & Lawrence, 2015), and refining outcome

83   assessment in alcohol research (Leffingwell et al., 2013).

84   Researchers have explored a variety of different methods for the continuous tracking of

85   drinking (Fairbairn & Kang, in press; Swift, 2003), but transdermal devices are currently those

86   with the firmest basis of empirical support for their viability as continuous alcohol biosensors.

87   Approximately 1% of alcohol consumed is diffused transdermally in the form of sweat and

88   insensible perspiration (Swift, 2003; Swift & Swette, 1992). Thus, similar to the manner in

89   which a breathalyzer estimates BAC by measuring the quantity of alcohol in expired air,

90   transdermal sensors might estimate BAC by examining alcohol in water vapor emitted from the

91   skin. Measured via a device that rests on the surface of the skin, transdermal assessment is

92   passive and unobtrusive. Correlations between transdermal alcohol concentration (TAC) and

93   blood alcohol concentration (BAC) tend to be strong (Giles et al., 1987; Luczak & Rosen, 2014;

94   Sakai, Mikulich-Gilbertson, Long, & Crowley, 2006). Yet, despite their promise, challenges

95   have emerged for transdermal monitors—including challenges associated with the available

96   devices themselves as well as those associated the data produced by these devices—and these

97   challenges have limited the widespread implementation of transdermal alcohol assessment within

98   research and also everyday drinking contexts.

99   Concerning challenges associated with the devices themselves, at the present time, the

100   only available transdermal monitors take the form of relatively large/bulky bracelets designed to

101   be worn around the ankle. Although previously some smaller wrist-worn transdermal devices

102   were accessible to researchers (e.g., the WrisTAS device)[1], at the current time, the Secure

103   Continuous Remote Alcohol Monitor (SCRAM) ankle bracelet is the only widely-available

104   wearable alcohol biosensor. SCRAM devices, which weigh about 6 oz and are approximately the

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[1] One of the first transdermal devices developed was the WrisTAS, marketed by Giner Labs, which was worn around the wrist as a watch (Leffingwell et al., 2013). However, this device was only used for research purposes, to our knowledge, and has not been made available to researchers for several years now.

105   dimensions of a large deck of cards, are mainly designed as abstinence monitors for use with

106   criminal justice-involved populations (see Figure 1). Data from SCRAM has been examined in

107   several dozen studies (Fairbairn et al., 2018; Sirlanci et al., 2018; see Leffingwell et al., 2013 for

108   a review), and associations between SCRAM-measured TAC and BAC have been generally

109   estimated as strong. SCRAM employs fuel cell technology whereby alcohol molecules are

110   translated into a measurable electrical current at the sensor. The large size of these bracelets is

111   partially attributable to the nature of the specific fuel cell employed, which requires a pump to

112   promote the active flow of air across the sensor, a feature that also limits the TAC sampling

113   interval to a relatively extended 30 minutes (Wang, Fridberg, Leeman, Cook, & Porges, in

114   press). The size, ankle positioning, and relatively sparse data produced by these devices appear

115   to be well suited for their application as abstinence monitors with non-voluntary populations.

116   However, since wearing SCRAM devices can produce discomfort and embarrassment (Barnett,

117   Tidey, Murphy, Swift, & Colby, 2011), the usefulness of these ankle monitors for voluntary

118   populations (e.g., as health behavior trackers among large populations of consumers) is severely

119   limited.

120   In addition to challenges associated with the transdermal devices themselves, another

121   important challenge surrounds the nature of the data produced by these devices—in particular,

122   delays between the time that alcohol is ingested and when it can be detected transdermally. TAC

123   is believed to lag behind BAC by a substantial margin, with the extent of this lag being typically

124   estimated as lasting at least 1-hour (Fairbairn & Kang, in press; Leffingwell et al., 2013), and

125   potentially as long as 3-4 hours (Marques & McKnight, 2009). Note that several of the more

126   pressing proposed applications of transdermal alcohol biosensors would require real-time or near

127   real-time estimation of drinking (Fairbairn et al., 2018; Fairbairn & Kang, in press)—e.g.,

128   researchers aiming to map everyday alcohol use with associated antecedent and/or consequent

129   behaviors in real time. Of note, while it is clear that some delay exists between BAC and TAC,

130   the exact extent of this delay is currently unclear. In estimating this delay, researchers have

131   mainly employed SCRAM ankle monitors, and have further examined delays nearly exclusively

132   by examining the relative timing of TAC/BAC peaks (Sakai et al., 2006; Swift, Martin, Swette,

133   Laconti, & Kackley, 1992). Regarding the former of these issues, since the permeability of the

134   skin and also the density of sweat glands differs on different areas of the body, the relationship

135   between BAC and TAC also differs depending on where on the body TAC is assessed (Swift,

136   2000). Indeed, a review of the literature indicates that the notion that TAC lags behind BAC by a

137   factor of 2-4 hours is derived entirely from studies employing ankle monitors (Fairbairn, Rosen,

138   Luczak, & Venerable, in press; Marques & McKnight, 2009), whereas studies employing wrist

139   sensors (e.g., the early WrisTAS device) have estimated substantially smaller lag times (Swift et

140   al., 1992; see Table 1 for a literature review of studies examining TAC in relation to objectively

141   assessed BAC). In addition, a more nuanced operationalization of lag-time—encompassing

142   other portions of the BAC curve beyond TAC/BAC peak—could aid in informing our

143   understanding of the relative timing of TAC vs. BAC.

144   Recently, a new generation of wrist-worn devices has emerged that leverages advances in

145   electronics and wireless communication in order to substantially reduce the size and increase the

146   comfort/attractiveness of transdermal alcohol monitors (Wang et al., in press). One such device

147   is BACtrack Skyn™. Skyn is a small device that includes a transdermal alcohol biosensor,

148   rechargeable battery, and a companion smartphone application. Skyn is worn on the inside of the

149   wrist—a position selected to increase its sensitivity and decrease lag to detected alcohol.

150   Currently in the prototype phase, Skyn is designed to be comfortable, user friendly, and socially

151   acceptable, similar to a Fitbit or smartwatch (see Figure 1). Like SCRAM, Skyn uses fuel cell

152   technology in order to assess TAC. Unlike SCRAM, however, Skyn devices do not require a

153   pump to generate air flow across the sensor and instead rely on passive airflow—a feature that

154   reduces the size and dimensions of the device and also facilitates more rapid TAC sampling, with

155   current prototypes allowing for sampling as frequently as every 20 seconds (Wang et al., in

156   press). While the new generation of transdermal alcohol sensors hold promise for use in research

157   as well as for widespread health behavior monitoring, these devices have not been examined in

158   controlled studies and so the relation of readings produced by these devices to ingested alcohol is

159   unknown.

160   In the current study, we employ laboratory methods to directly compare data produced by

161   two transdermal alcohol monitors—the widely-researched SCRAM ankle monitor and the newer

162   wrist-worn Skyn device. This study focuses on an examination of TAC over time among

163   participants administered a single fixed dose of alcohol, although we also include a subsample of

164   participants administered no alcohol by way of control. We used breathalyzer readings to

165   validate TAC measures—chosen as a noninvasive measure with a strong and well characterized

166   relationship with BAC (Bendtsen, Hultberg, Carlsson, & Jones, 1999; Jones & Andersson, 1996,

167   2003; Ramchandani, Plawecki, Li, & O'Connor, 2009). In light of the identified challenges

168   surrounding delays in the detection of alcohol via transdermal monitors (Leffingwell et al.,

169   2013), the primary aim of this research is to examine and quantify lag times between ingested

170   alcohol and TAC, operationalized through a range of metrics intended to capture various

171   positions on the BAC curve.

172   Note that the restricted alcohol dosing procedures employed in this study are well-suited

173   to addressing our primary aim of examining comparative lag times across transdermal sensors

174 under controlled conditions, whereas the limited variation in BAC produced by these procedures

175 mean that they are less well suited to quantifying the magnitude of BAC-TAC correlations.

176 Nonetheless, given that no prior study has quantified BAC-TAC correlations using this newest

177 generation of transdermal sensors, we also include a preliminary examination of BAC-TAC

178 correlations for both Skyn and SCRAM as a supplemental analysis.

179 Method

180 *Participants*

181 A total of 50 young social drinkers underwent experimental procedures. The final sample

182 of participants consisted of the 30 individuals for whom we were able to obtain breathalyzer,

183 SCRAM, and also Skyn readings for the experimental session (see later section on device

184 failures). This final sample of participants consisted of 25 participants assigned to the alcohol

185 condition and 5 participants assigned to the control condition. The average age of participants

186 was 22 years old (range, 21-28). Participants were 50% female (15 females and 15 males). Sixty

187 percent of participants identified as White, 23.3% as Asian, and 16.6% as multiracial (3.3%

188 African-American/Hispanic, 3.3% Hispanic/Asian, 3.3% White/Asian, 6.7% White/Hispanic).

189 Participants were required to be at least 21 years of age and no older than 30, to consume alcohol

190 regularly, and report being comfortable with the dose of alcohol administered in the study.

191 Exclusions included taking medications that might interact with alcohol, medical conditions for

192 which alcohol consumption was contraindicated, pregnancy in women, history of severe Alcohol

193 Use Disorder, or especially light drinking practices (see recommendations of the National

194 Advisory Council on Alcohol Abuse and Alcoholism, 1989 for alcohol-administration in human

195 subjects). On average, participants reported drinking alcohol on 10.13 days out of the past 30

196 (SD=4.73) and consuming an average of 4.90 drinks per occasion (SD=1.83).

197   ***Procedure***

198   Participants who successfully completed a phone screening were invited into the

199   laboratory for a beverage-administration session. All participants were required to abstain from

200   drinking alcohol for at least 12 hours prior to their laboratory session, and to refrain from eating

201   for 4 hours. Upon arriving in the laboratory, participants were breathalyzed (Intoximeters Alco-

202   Sensor IV) to ensure a 0.00 breath alcohol concentration (BrAC), and their weight and height

203   was assessed. Pregnancy was assessed in female participants via HCG urine test strip.

204   Participants were then given a light meal that was roughly adjusted for their weight.

205   Next, SCRAM monitors were positioned on the inside of participants' left ankles, worn

206   high up on the leg, snug against the calf. Skyn devices were positioned on the inside of

207   participants' left wrists. Both devices were then worn for a no-alcohol baseline period

208   (approximately 1 hour), during which baseline TAC readings were established and participants

209   completed questionnaires unrelated to the current study.

210   Participants were next administered their study beverages. Beverages were administered

211   in 3 equal parts over the course of 36 minutes, and participants were encouraged to consume

212   their beverages evenly over each of the three 12-minute intervals. Participants assigned to

213   receive alcohol received a dose intended to bring them up to the legal driving limit (.08%). The

214   precise amount of alcohol administered was adjusted for each individual's body water as

215   calculated based on formulas accounting for gender, height, age, and weight (Curtin & Fairchild,

216   2003; Watson, Watson, & Batt, 1981). Note that this dose of alcohol was originally chosen for

217   the purposes of the parent study investigating alcohol's effects on mood (e.g., Fairbairn et al.,

218   2018, 2015), but it also has utility for the proposed project, given potential applications of

219   wearable biosensors for determining driving safety. Control participants received an isovolumic

220   amount of a non-alcoholic beverage. Assignment to beverage condition was randomly

221   determined. Beverage intake was monitored via video to validate drink start time (see below) and

222   also to ensure even consumption across the 36-minute drink period.

223   Following beverage administration, participants in the alcohol condition provided

224   breathalyzer readings at approximately 30-minute intervals until they left the lab. During this

225   time period, participants engaged in a variety of study tasks, ranging from those requiring a

226   moderate amount of walking (e.g., between rooms in a lab) as well as those that were largely

227   stationary (e.g., speaking with another participant while seated). Participants in the control

228   condition were allowed to leave after study tasks were completed (3-4 hours after the end of

229   drinking). Participants administered alcohol were required to stay in the lab until their BrAC

230   dropped below .025%[2] and also their SCRAM TAC output registered at least one descending

231   value (generally between 5-7 hours post-drink—average BrAC among alcohol participants at

232   discharge .019%).

233   ***Data Processing and Analysis***

234   Skyn data was transmitted via Bluetooth from Skyn devices to BACtrack's custom

235   smartphone application, which was installed on our lab's ipod touch devices. The application

236   displays TAC readings in graphical form, and the raw data files can be exported in the form of

237   csv files via this application or BACtrack's internet-based data storage system. SCRAM data was

238   extracted using direct connect software and downloaded from SCRAMnet, a cloud-based server.

239   We analyzed latency of TAC values relative to the onset of drinking and BrAC curves

240   using the following three metrics: 1) latency to first transdermally detected alcohol; 2) time

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[2] In the current study, given the relatively substantial dose of alcohol administered, it was not feasible to keep participants in the lab until their BAC reached 0.00. Note that, including the pre-drink baseline, visits often lasted as long as 9 hours. Using the current procedures, we were able to capture the majority of the descending limb of the BAC curve.

241   elapsed between peak BrAC and peak TAC; and 3) latency to maximal cross-correlation across

242   TAC and BrAC curves. As an examination of these latency metrics among control participants

243   would not have been meaningful and, in some cases, would have been impossible (e.g., latency

244   to peak BrAC where BrAC values consist of all 0s), only participants assigned to the alcohol

245   condition were included in latency analyses. Note that data produced by SCRAM is standardized

246   such that it includes a natural zero starting value. In contrast, data produced by the Skyn

247   prototypes used in this study featured no standardized zero point, with baseline values varying

248   across Skyn files. With respect to time to first transdermally detected alcohol, for SCRAM TAC,

249   this was operationalized as the time elapsed from the very beginning of the participant drink

250   period to time of first non-zero SCRAM reading.[3] For Skyn TAC (files with no natural zero

251   point—see above), latency to first transdermally detected alcohol was operationalized via a

252   function that systematically tests each point in a series and automatically detects points of change

253   in the trend using a formula that minimizes the sum of the residual error and applies a penalty for

254   each change (MATLAB changepoint function; Killick, Fearnhead, & Eckley, 2012). Finally,

255   with respect to cross-correlations, these analyses were conducted at the level of the participant

256   and specifically targeted those assigned to receive alcohol (see below). In particular, cross-

257   correlation coefficients indexed the correlation between an individual's BrAC with that

258   individual's TAC (either Skyn or SCRAM) at various lag times (or latencies) over the course of

259   the session.[4] Since the sampling intervals for BrAC and SCRAM TAC were relatively sparse

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[3] Note Alcohol Monitoring Systems (AMS) itself uses a much higher threshold (at least .02% TAC) when processing SCRAM data files in order to identify alcohol episodes. This relatively high TAC threshold is adopted in order to reduce the risk for false positives, which were not a concern in the current study.

[4] Cross-correlation is a metric for assessing the similarity of two time series as a function of the level of displacement between the series. A cross-correlation analysis will produce the value of the correlation of two time series across multiple different "lags" or displacement levels—e.g., Skyn value at time t with BrAC at t-1, Skyn value at time t with BrAC at t+1, contemporaneous Skyn and BrAC, etc. The maximal cross-correlation—or the time lag at which the correlation between the two time series is at its peak—can be used to assess the level of displacement between the two time series.

260   (~30 minutes) when compared with Skyn (1 minute), BrAC and SCRAM data was interpolated

261   from sampled values such that a file with minute-level estimates of BrAC, SCRAM TAC, and

262   Skyn TAC was produced for each participant spanning the time period from the beginning of the

263   drink period to last BrAC reading (Fritsch & Carlson, 1980; Sidek & Khalil, 2013). Cross-

264   correlation analysis was applied to each participant file and the lag time that maximized the

265   value of the cross-correlation function between BrAC and TAC (both Skyn and SCRAM) was

266   recorded for each participant (Gottman, 1981). Paired t-tests were used to compare lag times for

267   Skyn TAC and SCRAM TAC.

268   The association between BrAC and transdermally detected alcohol was assessed using

269   the following three metrics: 1) Correlation in peak BrAC and TAC values across participants; 2)

270   Correlation in area under the curve for BrAC and TAC across participants; 3) Maximal value of

271   cross-correlation between BrAC and TAC for each participant. For the purposes of calculating

272   peak and area under the curve values, Skyn data was centered and standardized by subtracting

273   the start value (reading taken at the initiation of the drink period) from all subsequent readings.

274   All participants (alcohol and control) were included in the analysis of peak values and area under

275   the curve—which examine variation between participants—whereas only participants in the

276   alcohol condition were included in cross-correlation analyses—which examine variation within

277   participants over time, and so variability at the within-subject level is required. Area under the

278   curve for BrAC, Skyn, and SCRAM data was calculated by summing all data points from the

279   beginning of the drink period to the last moment that a BrAC reading was taken. Pearson

280   correlation coefficients were used to examine associations between peak values and area under

281   the curve for BrAC and TAC. Maximum cross-correlations between BrAC data and TAC (see

282   above) were calculated for each participant and then Skyn and SCRAM correlations for each

283   participant were compared using paired t-tests.

284   Results

285   *Descriptive and Device Statistics*: Among those assigned to receive alcohol, average peak

286   BrAC was .08% (*SD*=.01; *Range* .06-.12). Five different Skyn prototype devices and 13 SCRAM

287   ankle monitors were used for this research. The five Skyn devices employed included 3 older

288   generation prototype devices (manufactured in 2016) and 2 newer generation prototype devices

289   with improved Bluetooth connectivity and other additional features (manufactured in 2018).

290   Among alcohol participants, over the course of the entire lab session, the average number of

291   BrAC readings collected per participant was 11 (*SD*=1.6), the average number of SCRAM TAC

292   readings was also 11 (*SD*=1.4), and the average number of Skyn TAC readings was 309

293   (*SD*=44.3).

294   In Figure 2, we provide visualizations of data from all alcohol (P1-P25) and control

295   participants (P26-30) during the laboratory session. In line with data produced in prior studies,

296   visual inspection of these data suggests that there exists variability in both Skyn and SCRAM

297   measured TAC that appears to be unconnected with alcohol consumption. Nonetheless, among

298   participants assigned to receive alcohol, TAC broadly mirrors the characteristic BAC curve,

299   ascending with alcohol ingestion and then descending with the passage of time following

300   ingestion.

301   *Device Failure Rate*: Note that Skyn devices used in this study were prototypes, and rates

302   of failure of both the devices and the accompanying smartphone application were relatively high.

303   A total of 9 Skyn files were either incomplete, blank, or unusable due to device failure (3 files

304   were completely blank for unknown reasons, 3 files consisted of an entirely flat line with no

305   oscillation, and 3 files were blank or severely truncated due to battery failure). An additional 10

306   Skyn files were lost during the initial stages of this project as our team learned to work with

307   these delicate prototypes.[5] In contrast, SCRAM devices, which are not in the prototype phase,

308   produced only one unusable (flat line) file within the conduct of this research. In sum, failure

309   rates for Skyn prototypes ranged from 18%-38% (depending on metric), whereas the failure rate

310   for SCRAM was 2%. Data presented below reflects that derived from our final sample of

311   participants—individuals for whom we were able to obtain BrAC, SCRAM, and also Skyn data

312   (see methods section).

313   *TAC Latency*: With respect to latency to first detected alcohol, both Skyn TAC and

314   SCRAM TAC appeared to perform relatively well, detecting alcohol within 30 minutes of the

315   initiation of the drink period. Time to first detected alcohol via Skyn was 22.08 (*SD*=12.38)

316   minutes[6] and was very similar for SCRAM at 22.52 (*SD*=13.03) minutes. The difference between

317   these values was non-significant, $t(24)=.14$, $p=.891$. See also Table 2.

318   BrAC readings reached their peak an average of 77.28 (*SD*=30.34) minutes after the start

319   of drinking. Skyn TAC readings peaked an average of 131.52 (*SD*=32.90) minutes after the start

320   of drinking (54 minutes after peak BrAC), and SCRAM TAC readings peaked an average of

321   197.20 (*SD*=42.60) minutes after the start of drinking (120 minutes after peak BrAC). The

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[5] The Bluetooth connection feature of the Skyn devices naturally disconnected from the accompanying smartphone application throughout the visit as participants moved from room to room. In order to reconnect and generate a datafile for some of these Skyn prototypes, it was necessary to first close and then re-open the accompanying smartphone application and also disconnect/reconnect the device from Bluetooth—a quirk we discovered only with trial and error after experiencing some data loss.

[6] In addition to the MATLAB changepoint function, we also attempted this analysis using one additional operationalization—defining time to first detected alcohol as 10 consecutive Skyn readings above the initial baseline value. Using this alternative operationalization, the average time to first detected alcohol via Skyn was 17.72 minutes (SD=11.51). However, given that the choice of "10 values" was somewhat arbitrary, we present the automated MATLAB approach (above) for the purposes of final analyses.

322   difference in lag time between peak Skyn TAC and peak SCRAM TAC emerged as highly

323   significant: M_{diff}=65.68 minutes (SD=51.27), $\underline{t}$(24)=6.41, p<.001.

324   Finally, when cross-correlation coefficients were examined, the average latency of

325   maximal cross-correlation between BrAC and Skyn TAC was 23.88 (SD=26.11) minutes. The

326   average latency of maximal cross-correlation between BrAC and SCRAM TAC was 68.56

327   (SD=36.83) minutes. The difference in lag time between peak Skyn TAC and peak SCRAM

328   TAC emerged as highly significant: M_{diff}=44.68 minutes (SD=43.09), t(24)=5.18, p<.001. Note

329   that these values reflect the average lag time across all portions of the BAC curve measured in

330   the current research—representing the majority, although not the entirety, of BAC/TAC curves

331   (see methods). See Table 3 for cross-correlation lag times presented at the level of the device.

332   *TAC-BrAC Associations*: Here we provide preliminary information concerning the

333   association between BrAC, Skyn TAC and SCRAM TAC when dosing range in the alcohol

334   condition is highly restricted (see above). Across all 30 participants, there was a strong and

335   significant positive correlation between peak BrAC and peak Skyn TAC values, r=.77, n=30,

336   p<.001. There was also a strong significant correlation between peak BrAC and peak SCRAM

337   TAC, r=.56, n=30, p=.001. Participants who reached a higher peak BrAC also had higher peak

338   TAC values, as measured using Skyn and also SCRAM. Concerning area under the curve, there

339   was a strong and significant positive correlation for BrAC and Skyn TAC, r=.79, n=30, p<.001,

340   as well as for BrAC and SCRAM TAC, r=.60, n=30, p<.001. Finally, in cross-correlation

341   analyses examining within-participant change over time among alcohol participants examined as

342   time series (see above), the average maximal cross-correlation between BrAC and Skyn TAC

343   was .60 (SD=.15). The average maximal cross-correlation between BrAC and SCRAM TAC was

344   .51 (SD=.12). The difference between these correlations emerged as statistically significant:

345 M_{diff}=.09 (SD=.20), t(24)=2.38, p=.026, with cross-correlations being higher for Skyn vs.

346 SCRAM. Note that results of analyses examining area under the curve and also cross-

347 correlations (although not peak values) should be interpreted with incomplete TAC/BAC

348 trajectories and also differential lag times for Skyn vs. SCRAM in mind. See Table 3 for cross-

349 correlations at the level of the device.

350   Discussion

351   Transdermal alcohol sensors represent a promising method for continuous, unobtrusive

352 measurement of alcohol consumption. But the measurement of alcohol consumption

353 transdermally has been associated with significant challenges, including those associated with

354 devices themselves as well as the delay in data produced by these devices. The current research

355 represents the first systematic examination of data produced via a new generation transdermal

356 device that features a compact, wrist-worn design, relatively rapid TAC sampling, and

357 smartphone connectivity. Specifically, using data derived from a controlled dosing context and

358 varied metrics for capturing TAC latency, we examined lag times between ingested alcohol and

359 transdermally detected alcohol among participants wearing both the SCRAM ankle monitor and

360 a prototype of the newer wrist-worn Skyn device. Both Skyn and SCRAM showed initial

361 temporal sensitivity to ingestion of a moderate dose of alcohol, detecting alcohol within 30

362 minutes of first consumption. As time progressed across the drinking episode, the wrist-worn

363 Skyn device emerged as generally faster in its response to alcohol ingestion compared with the

364 ankle-worn SCRAM. Specifically, TAC measured using Skyn reached its peak over an hour

365 prior to TAC measured using SCRAM (54 minutes after peak BrAC for Skyn vs. 120 minutes

366 after peak BrAC for SCRAM). On average, when all measured portions of the BAC curve were

367 considered via time-series models, Skyn lagged behind BrAC by approximately 24 minutes,

368   whereas the average lag between BAC and SCRAM was significantly longer at 69 minutes. In

369   other words, in time-series models, the lag time between Skyn and SCRAM emerged as nearly

370   double the duration of lag time between Skyn and actual BrAC. Finally, this study also provides

371   some information on the validity of the wrist-worn prototype in terms of dose-response—

372   although associations captured within this study should be considered preliminary (likely

373   dampened) due to the restricted dosing range as well as the slightly truncated TAC/BAC

374   trajectories captured in our lab session. Note that Skyn devices used in this study were

375   prototypes, and data captured with both Skyn and SCRAM devices demonstrated variability in

376   TAC that appeared to be unrelated to BrAC. Nonetheless, correlations between Skyn TAC and

377   BrAC captured within this study were large in magnitude and tended to exceed correlations

378   between BrAC and SCRAM TAC.

379   The lag time between ingested alcohol and transdermally detected alcohol is typically

380   estimated as being at least 1 hour in duration (Leffingwell et al., 2013), with some studies

381   estimating this delay as lasting up to 4 hours (Marques & McKnight, 2009). Note that these

382   lengthier delay estimates have been derived from studies employing the SCRAM ankle monitor,

383   and have further not typically examined lag times at points on the BAC curve beyond peak

384   values (Marques & McKnight, 2009; Sakai et al., 2006; Fairbairn & Kang, in press; See Table 1

385   for a review). The prolonged nature of such delays might preclude certain real-world applications

386   of transdermal alcohol sensors—e.g., a drinker wishing to assess his/her safety for operating a

387   motor vehicle. As with past research, data from the current study continued to provide evidence

388   for a delay in the transdermal detection of alcohol when compared with BrAC. However, here,

389   when examined across the entire sampling interval investigated in this research—which

390   encompassed the majority (although not the entirety) of the BAC curve—the average lag time

391   between Skyn-estimated TAC and BrAC was less than 30 minutes, significantly smaller than that

392   estimated via SCRAM. In the future, applications of advanced machine learning algorithms—

393   with the ability to predict future values based on sequences of current values—might ultimately

394   be applied to TAC data to further reduce the extent of this lag (Mandic & Chambers, 2001).

395   In addition to its implications for the understanding of lag times between BAC and TAC,

396   this research also contributes to the literature by providing preliminary information on the

397   validity of a relatively compact, wrist-worn sensor. To date, a barrier to the widespread

398   implementation of transdermal biosensors has been the relatively large/bulky nature of extant

399   transdermal devices. At the present time, the SCRAM ankle monitor is the only readily available

400   transdermal sensor. SCRAM, and similar devices, will likely continue to have an important place

401   in assessing drinking among criminal-justice involved populations and for some research and

402   clinical applications, and, at the current time, SCRAM remains the most reliable available

403   transdermal sensor. However, the relatively bulky design and ankle positioning of this device

404   limit its usefulness outside of specific clinical, criminal justice, and research applications and

405   preclude its implementation among broad populations of drinkers interested in tracking their

406   health behaviors. Thus, although approximately half of the world's population drinks alcohol

407   (WHO, 2014), with 27% of US adults reporting at least one episode of binge drinking in the past

408   month (SAMHSA, 2015), only a subsample of these individuals are served by current

409   transdermal technology. Note that the current study examined TAC data in response to a fixed

410   dose of alcohol, restricting the range of BACs and so likely leading to attenuated estimates of the

411   associations between TAC and BAC. Nonetheless, despite the fixed dosing procedures,

412   associations between Skyn TAC and BAC emerged as strong. Thus, by providing initial data for

413   the validity of a compact, wrist-worn sensor, the current study takes an important first step

414   towards providing an attractive, wearable device for everyday drinkers seeking to monitor their

415   alcohol consumption.

416   Although the current project represents an important first step to addressing specific

417   challenges associated with the transdermal detection of alcohol, many other key challenges lie

418   ahead before these devices are ready for real-world implementation. As noted above, similar to

419   data produced by prior studies (Leffingwell et al., 2013), data from the current study indicate that

420   the BAC-TAC correlation is strong, but yet this correlation is not a perfect one and so some

421   portion of the variation in TAC remains as yet unexplained. As it pertains to Skyn data, some of

422   this unexplained variability is likely attributable to the fact that the devices used in this study

423   were hand-assembled prototypes, and so this variability may diminish with device development

424   as prototypes improve and machine-made devices become available. It is also possible that some

425   of this unexplained variability may simply be a characteristic intrinsic to transdermal alcohol

426   measurement. Note that current Skyn prototypes collect data on not only TAC, but also include

427   temperature and accelerometer gauges—measures that may account for some portion of the

428   variability in the BAC-TAC relationship—and algorithms that incorporate information from all

429   of these gauges simultaneously may ultimately be able to provide a closer approximation of

430   exact BAC values. Further, the relationship between TAC and BAC is believed to vary

431   depending on both individual-level factors (e.g., the thickness of an individual's skin) as well as

432   situation-level factors (e.g., degree of ambient humidity). Note that it is possible that the extent

433   of variation in the BAC-TAC relationship has been over-estimated due to a tendency of prior

434   studies to rely on data from the SCRAM monitor, the ankle positioning of which might lead to

435   increased variation in the distance between sensor and skin (e.g., sliding from sitting snug

436   against the calf to hanging loosely around the ankle bone as participants walk)—a factor that has

437   been theorized to have an important impact on the BAC-TAC relationship (see Anderson &

438   Hlastala, 2006). Nonetheless, it will be critical to conduct research examining large and diverse

439   samples of participants, in addition to extensive research in real-world contexts featuring

440   fluctuation in ambient conditions, in order to further disentangle the relationship between TAC

441   and BAC. These future studies will also need to address the issue of potential "false positive"

442   TAC values produced by environmental alcohol, considering sensitivity and specificity as well

443   as the reliability of the Skyn over time and across devices. Relatedly, data from the current Skyn

444   prototype represents a raw value reflecting electrical current detected at the transdermal sensor

445   and has not been standardized to include a meaningful zero metric or reflect a scale comparable

446   to BAC. Thus, in the current study, we examine correlations between Skyn TAC and BAC,

447   rather than estimating the accuracy of measurements produced from the Skyn device. Skyn data

448   in the current study was standardized for each individual/device combination by subtracting out

449   the baseline value. Translating Skyn data into estimates along a standardized metric—and

450   accounting for factors that might lead to differential baseline values across different

451   device/individual combinations—is a task for future research.

452   Although the current study does suggest that the lag time between BAC and TAC

453   diminishes when TAC is measured using Skyn, the question of mechanism is unaddressed. The

454   extent to which this effect is explained by characteristics of the device (e.g., method of

455   measurement, sampling interval) or by the body positioning of the device (e.g., relative

456   distribution of sweat glands, permeability of skin) is left for future research to explore. It's also

457   worth noting that the hand-assembled Skyn prototypes employed in this study yielded a

458   relatively high failure rate (18%-38% vs. 2% for SCRAM). More durable and reliable prototypes

459   will likely be required before extensive field testing is feasible. Thus, at the current time,

460   SCRAM is still the most reliable transdermal alcohol sensor.

461   Finally, note that participants in the current study left the laboratory once their BrAC had

462   descended below .025% and their TAC had also begun to descend (see methods). Thus, although

463   these methods did capture the majority of BAC and TAC curves for participants enrolled, these

464   curves were not complete. Thus, analyses presented here that might be impacted by such

465   incomplete curves—area under the curve calculations and also cross correlation analyses—

466   should be interpreted with these truncated curves in mind. Future research should examine

467   complete TAC/BAC curves when feasible.

468   *Conclusion*

469   A wearable alcohol biosensor has the potential to fill a tremendous public health gap.

470   The path towards developing such a biosensor has been lengthy and involved formidable

471   challenges. Recent devices have been developed that leverage advances in miniaturization and

472   electronics, and rigorous research of such devices, employing multiple methods and large human

473   samples, offer the possibility of at last producing a viable alcohol biosensor and, importantly,

474   clarifying its potential place in the arsenal of techniques aimed at better researching, preventing,

475   and treating alcohol use disorders.

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477   References
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616   **Figure Legends**

617   *Figure 1*. AMS SCRAM ankle bracelet (left) and BACtrack Skyn wrist monitor (right) displayed

618   side-by side. The top panel displays these devices as worn on ankle/wrist, whereas the bottom

619   panel displays them to scale. The approximate weight of the devices is 6oz (SCRAM) and 1oz

620   (Skyn prototype), respectively.

621   *Figure 2*. Skyn prototype, SCRAM, and BrAC data for each of the 25 participants assigned to

622   receive alcohol (P1-P25) as well as the 5 no-alcohol control participants (P26-P30). Data reflects

623   the entire period of assessment, beginning from the moment just prior to first alcohol

624   consumption (beginning of the drink period) to the final BrAC reading. For this visualization of

625   Skyn data, data was standardized by subtracting the lowest value for each participant file, and a

626   30-minute moving average window was also applied.

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Table 1.
Studies examining validity of transdermal alcohol sensors using objective assessment techniques
(BrAC/BAC)

Study	N	Type	Device	Locat	Alc Meas	Lag (min)	r's
Giles et al., 1987	19	Lab	Unspec	Palm	BAC	NR	.94-.99
Swift & Swette, 1992	15	Lab	WrisTAS	Arm	BrAC	30	.61-.96
Davidson, Camara, & Swift, 1997	12	Lab	Unspec	Arm	BrAC /BAC	NR	.52-.70
Dougherty et al., 2012	22	Lab	SCRAM	Ankle	BrAC	NR	.70-.99
Hill-Kapturczak et al., 2014	19	Lab	SCRAM	Ankle	BrAC	NR	NR
Hill-Kapturczak et al., 2015	21	Lab	SCRAM	Ankle	BrAC	129	.87
Wang, Fridberg, Leeman, Cook, & Porges, 2018	2	Lab	Skyn /Tally	Wrist	BrAC	75 /55	NR
Sakai et al., 2006	20	Lab	SCRAM	Ankle	BrAC	150	.49-.84
Fairbairn et al., 2018, in press	48	Lab/Amb	SCRAM	Ankle	BrAC	130	NR
Marques & McKnight, 2009	22	Lab/Amb	WrisTAS/ SCRAM	Wrist/ Ankle	BrAC	137/ 270	NR
Sakai et al., 2006	24	Amb	SCRAM	Ankle	BrAC	NR	NR
Luczak & Rosen, 2014	1	Lab/Amb	WrisTAS	Wrist	BrAC	NR	NR

The top section of this table lists studies conducted only in the laboratory, whereas the bottom section lists studies that included an ambulatory (field) assessment arm. Where a study contained both laboratory and ambulatory arms, but examined distinct groups of participants within these arms (e.g., Sakai et al., 2006), the study is listed under both sections of the table.

Note that, in the case of some of the studies listed above, data from the same sample were included in more than one publication (e.g., Fairbairn et al., 2018, in press). In such cases, only the citation for the parent (first) publication is listed in the table. Studies featuring devices that were not clearly "wearable" (e.g., Kamei et al., 1998) and also studies featuring sweat patches (e.g., Phillips, 1984) are not included.

Lab=laboratory study; Amb=Ambulatory study; Unspec =transdermal device not named; Locat=Body position of the transdermal device; Alc Meas=How BAC was measured in the study; BAC=Direct measure of BAC via blood or plasma; BrAC=Breathalyzer; Lag=time (in minutes) between peak BAC and peak TAC; NR=Not reported; r's=correlation coefficients between TAC and BAC

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Table 2.
Latency to Transdermal Detection of Alcohol

	Mean Minutes (SD)	Paired t-test (Skyn vs. SCRAM)
Latency to First Detection		
SCRAM TAC	22.52 (13.03)	
Skyn TAC	22.08 (12.38)	$t(24)=.14, p=.891$
Latency to Peak		
BrAC	77.28 (30.34)	
SCRAM TAC	197.20 (42.60)	
Skyn TAC	131.52 (32.90)	$\underline{t}(24)=6.41, p<.001$
Max Cross-Correlation Lag		
BrAC and SCRAM TAC	68.56 (36.83)	
BrAC and Skyn TAC	23.88 (26.11)	$t(24)=5.18, p<.001$

SD=Standard deviation. TAC=Transdermal alcohol concentration. BrAC=Breath alcohol concentration.

All latency values above are calculated with respect to the beginning of the drink period for alcohol participants (N=25). Cross-correlations were calculated based on data collected from the beginning of the drink period until discharge, which occurred once BrAC had dropped below .025% and TAC had also begun to descend (average BrAC at discharge .019%)

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Table 3.

Device-Level Maximal Cross-Correlation Values and Lag Times between BrAC and TAC

Device-Level Cross-Correlations for Skyn

Device ID	N	Mean Max Cross-Correlation (SD)	Mean Max Cross-Correlation Lag (SD)
7AB3	8	.66 (.16)	17.75 (10.98)
B6B3	2	.40 (.18)	32.50 (7.78)
18	3	.58 (.03)	22.00 (14.18)
9	2	.50 (.26)	16.50 (23.34)
0DB5	10	.62 (.12)	29.10 (38.98)

Device-Level Cross-Correlations for SCRAM

24141	2	0.50 (0.05)	26 (31.11)
80002	1	0.42	57
114798	2	0.47 (0.01)	72 (11.31)
114888	4	0.43 (0.08)	67 (25.81)
115307	4	0.53 (0.16)	64.50 (24.37)
115411	1	0.69	48
115503	1	0.52	180
115887	1	0.57	93
117117	1	0.56	71
126571	1	0.61	118
127392	4	0.52 (0.21)	48.75 (33.08)
127453	1	0.50	49
127773	2	0.51 (0.06)	90.50 (41.72)

SD=Standard deviation. TAC=Transdermal alcohol concentration. BrAC=Breath alcohol concentration. N=Number of participants who wore this device. Mean Max Cross-Correlation Lag is presented in minutes. Devices worn by only one participant list no standard deviation.

Cross-correlations refer to within-subject correlations between TAC (measured either using Skyn or SCRAM devices) and BrAC for alcohol participants (N=25) measured over time during the course of the lab session. Cross-correlations were calculated based on data collected from the beginning of the drink period until discharge, which occurred once BrAC had dropped below .025% and TAC had also begun to descend (average BrAC at discharge .019%). Cross-correlations listed under Skyn devices represent associations between BrAC and Skyn-measured TAC, and cross-correlations listed under SCRAM devices represent associations between BrAC and SCRAM-measured TAC.

Of the Skyn devices listed above, 7AB3, B6B3, and 0DB5 represent older generation Skyn prototypes (2016), whereas devices 18 and 9 represent newer generation prototypes (2018).

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