Correspondences

Pupil responses allow communication in locked-in syndrome patients

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For patients with severe motor disabilities, a robust means of communication is a crucial factor for their well-being [1]. We report here that pupil size measured by a bedside camera can be used to communicate with patients with locked-in syndrome. With the same protocol we demonstrate command-following for a patient in a minimally conscious state, suggesting its potential as a diagnostic tool for patients whose state of consciousness is in question. Importantly, neither training nor individual adjustment of our system's decoding parameters were required for successful decoding of patients' responses.

Pupil size is controlled by the complementary activity of muscles innervated by parasympathetic and sympathetic projections. In addition to the pupil dilation known to accompany emotionally arousing events, more subtle pupil dilation events have been linked to a variety of mental functions [2], including decision-making [3]. Our paradigm used mental arithmetic as a tool for patients to control and maximize their pupil dilation to signal their responses [4]. Each trial had the following structure (Figure 1A): an experimenter read out a factual question with a clear yes/no answer, such as "Is your age 20?". The correct answer was known for all questions, and 'correct decoding' refers to this ground truth. Five seconds after the question ended, a computer voice read out the first answer option: "yes" in half of the trials, "no" in the other half. Simultaneously with the onset of this read-out, a calculation task was presented in large font (150 pt) on a computer screen placed approximately one to two metres from the participants, and remained visible for a fixed duration. After this 'first calculation interval', the computer voice read out the alternative option ("no"/"yes"), and simultaneously a second calculation task was presented on the screen. This calculation remained visible for the same duration as the first ('second calculation interval'). Participants were asked to perform the calculation presented in the interval that accompanied the correct answer, and to ignore the calculation accompanying the incorrect answer. Throughout a session, each question was asked twice with the order of answers reversed. All trials were treated independently for all analyses except for the assessment of consistency.

The duration of the calculation intervals and the difficulty of the arithmetic problems were set for each individual prior to each experiment and remained fixed thereafter (see Supplemental Experimental Procedures). All other experimental parameters and analysis protocols were first established in healthy participants and then remained unchanged for all patients. In particular, the first 1.5 seconds of each calculation interval were discarded in all patients based on healthy participant data to reduce any possible impact of pupil responses to changes in the visual stimulus depicting the calculation task.

To reduce the pupil dynamics across a trial to a single value, we first subtracted pupil size in the first calculation interval from pupil size in the second. To the resulting difference trace (Figure 1B, black trace), a linear regression was then fit (Figure 1B, red line). All further analysis was based on the slope of this regression line ('pupil slope'). Pupil slope is by definition larger if the pupil dilates predominantly in the second interval, and smaller if pupil dilates predominantly in the first interval. Hence, if pupil control through mental arithmetic is successful [4], large pupil slopes correspond to the answer option presented second (Figure 1B, red), small pupil slopes to the option presented first (Figure 1B, blue). Success of decoding based on pupil slope is quantified in each individual by the area under receiver operator characteristics curve (AUC). Six healthy participants performed 30 trials each. For each individual, decoding of responses based on pupil slope was near ceiling (AUC range: 84–99%; Figure 1C, green) and each individual showed an AUC significantly different from chance (50%).

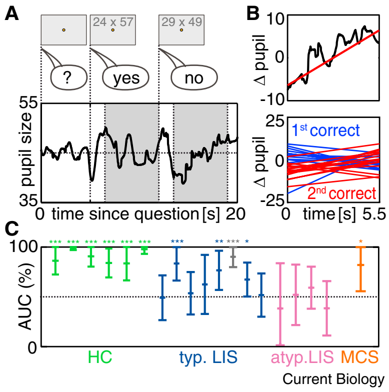

Figure 1. Pupil-size communication with locked-in syndrome patients.
(A) Example trial. *Top*: trial layout, *bottom*: corresponding pupil trace of typical locked-in syndrome patient #2. Calculations were presented above a fixation mark, which remained visible on the screen throughout the trial to minimize refocusing and thus re-accommodation; grey shading indicates part of the calculation intervals used for analysis; the unit of pupil size is pixel^2 (see Supplemental Experimental Procedures). (B) *Top*: the slope of the difference signal (black trace) is determined by linear regression (red line), and referred to as pupil slope of the trial; *bottom*: all pupil slopes for the example patient split by questions for which the correct answer corresponded to the first interval (blue) or the second (red). (C) Areas under the receiver operator characteristics curve (AUCs) with 95% confidence intervals for decoding of response from pupil size (***$p<0.001$; **$p<0.01$; *$p<0.05$). *Green*: healthy participants (HC), *blue*: patients with typical locked-in syndrome, second session of patient #5 in gray, *magenta*: patients with atypical locked-in syndrome, *orange*: patient in a minimal conscious state performing command following.

The system was then tested in seven 'typical' locked-in syndrome patients with brainstem stroke etiology (normal cognitive function, no supratentorial lesions, Supplemental Table S1). Five patients performed 30 trials, one patient (#4) 18 trials and another (#6) 40 trials. Three patients were significantly different from chance at an individual level (AUCs: 67%, 77%, 84%; Figure 1C, blue). For a further three patients decoding performance was above chance but failed to reach significance. Post-hoc analysis indicated that two out of these three would also reach significance individually (AUCs: 71%, 73%) by adjusting a single parameter — the onset of the interval used to compute the pupil slope (see 'Alternative measures' in the Supplemental Results). A single patient (#5) was retested on a different day (Figure 1C, grey), and showed improved performance in the second session (90%) as compared to the first (77%).

Four 'atypical' locked-in syndrome patients with supratentorial brain injuries were tested. Of those only one (#3) completed all 30 trials, while the others performed 10 (#1) or 18 (#2, #4) trials before showing obvious signs of fatigue. Decoding performance for all four supratentorial locked-in syndrome patients fluctuated around chance (AUC range: 38–59%; Figure 1C, magenta) and none of them reached significance individually.

When comparing the decoded answer for the two occurrences a patient is asked the same question, inconsistent responses are by definition uninformative, even if (as in practical application) ground truth is unknown. For consistently decoded questions — the system indicated either "yes" or "no" both times for a fixed cut-off point; for details see 'Inter-block consistency' in the Supplemental Results —decoding was *always* correct with respect to ground truth in the three significantly decoded patients and, with one exception, in all healthy participants. Of the other four locked-in syndrome patients that were asked all questions twice, but did not show significant decoding, two still had all (4/4) or all but one (6/7) of the consistently decoded questions correct, though these results in the absence of statistical significance in decoding performance need to be considered with caution. Nonetheless, for our sample of questions in significantly decoded patients, by simply asking the same question twice and considering both jointly, the system's decoding was either correct or known to be uninformative, but never incorrect.

In the case of a non-communicative minimally conscious state patient, it became evident during the first couple of trials that he did not follow task instructions. Hence, instead of relying on the patient's free choice of interval (answer), he was instructed by one experimenter when he had to perform the calculation. Of the 13 trials he performed in this command-following mode, the response could be decoded from the pupil slope at an AUC of 82%. Despite the low number of trials, this result was significantly above chance level (Figure 1C, orange).

Our data provide proof-of-principle for pupil dilation as means of communication in severely motor-impaired patients. With no training and no parameter adjustment to the individual, up to 90% decoding performance was reached. Rather than utilizing the response to a decision as such [3], which could, for example, be confounded with the difficulty of the decision, our paradigm allows patients to actively control their pupil dilation by modulating their mental effort. Whether or not patients actually solve the problem posed is of little relevance. Rather, mental arithmetic provides one robust way (amongst many) to manipulate one's pupil dilation, even if — as in the minimally conscious state patients — no active engagement in the task is otherwise apparent.

Typical brain-computer-interfaces either use invasive methods [5] or EEG in combination with machine-learning techniques [6] to measure neural activity. Besides the risk of the surgical procedure or the maintenance demands (for example, electrode cleaning), with few exceptions [7] training with the individual is required. Pupil size controlled through mental effort offers an alternative path, reflecting (neuro-)physiological activity that is easy and inexpensive to measure in daily life, requiring nothing but a bedside camera. Furthermore, in cases of complete locked-in syndrome, approaches that require some residual volitional movements, such as sniffing [8] or blinking [9], are by definition unsuitable [10]. In contrast, our system may in principle be tested in patients in complete locked-in syndrome without training prior to an acute insult. Finally, the minimally conscious state data demonstrates our system's potential usefulness as an additional diagnostic tool to assess a patient's state of consciousness.

Supplemental Information

Supplemental Information includes results, experimental procedures, two figures and one table and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2013.06.011.

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