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Crossed–uncrossed difference in simple reaction times to lateralized flashes: between- and within-subjects variability

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Abstract

In unimanual reaction times (RT) to lateralized flashes, contralateral responses tend to be slower than ipsilateral responses. This has been called Crossed–Uncrossed Difference (CUD). The CUD tends to show variability across subjects and across studies, but until now the stability of the CUD in an individual subject has not been investigated. To address the role of inter- and intra-subject variability in the CUD, three normal right handers were tested over 50 experimental sessions of 800 trials each, for a total of 40,000 trials of simple reaction times to lateralized flashes. In each subject, CUDs were computed for each session, over two, three, or more sessions, and over the entire dataset. These CUDs were then compared to the CUDs obtained in a group of 15 normal right handers, each tested once in a single session. Results show that: (i) CUD variability across several sessions in a single subject mimics the variability observed in a sample of subjects tested in a single session; (ii) this variability is considerably reduced when the CUD is computed over at least 2400 trials per subject; (iii) CUDs computed over 2400 and up to 12,000 of trials tend to be extremely similar (~2 ms) across the three subjects tested here; (iv) when reaction times are ordered from the fastest to the slowest and divided into bins, the CUD is remarkably stable over the entire reaction time distribution; and (v) in contrast to the variability of the CUD, the variability for crossed and uncrossed responses across several sessions in a single subject is small and does not mimic the variability observed in a sample of subjects tested in a single session. Taken together, these data suggest that the intersubject variability in the CUD observed in single experimental sessions does not represent a reliable intersubject difference and that the CUD computed over thousands of trials reflects hard-wired mechanisms of callosal transmission.

Keywords: Corpus callosum; Interhemispheric transmission time; Visuomotor integration

1. Introduction

The Crossed–Uncrossed Difference (CUD) is a widely studied chronometric parameter in laterality literature [2,4,6–8,10,14,18,21,25]. It refers to the difference in response times between the 'uncrossed' condition, in which sensory stimuli and motor responses are ipsilateral, and the 'crossed' condition, in which sensory stimuli and motor responses are contralateral. The canonical interpretation of the CUD in simple reaction time tasks is that it reflects time taken to transfer information from the cerebral hemisphere that receives the sensory stimulus to the cerebral hemisphere that controls the motor response. In choice response time tasks the CUD may reflect more complex phenomena, such as 'spatial compatibility' when selection of motor response is required [3,4,11–13].

Evidence in favor of the canonical, or hard-wired hypothesis, that in simple visuomotor tasks the CUD reflects interhemispheric transfer time, is that in this task normal subjects have a CUD of 3–4 ms, whereas patients born without the corpus callosum have a CUD from 10 to 20 ms, and finally patients who

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underwent complete surgical section of callosal fibers have a CUD from 30 to 60 ms [8,14,18]. This canonical view has been challenged on both theoretical [15] and empirical grounds [16,22,24], suggesting that the CUD may represent, instead, differential hemispheric activation, such that the hemisphere that receives the sensory stimulus is more activated and thus responds faster than the contralateral hemisphere. One of the typical features of the CUD that may have led to these alternative, functional hypotheses, and that prompted systematic investigation of its electrical scalp recordings correlates [22,24], as well as generated comprehensive meta-analyses and reviews [4,7,18], is its large variability. Surprisingly, to the best of our knowledge, only one previous study has addressed the reliability of CUD [25]. In that study, St John and colleagues observed that the reliability of the CUD is larger for males than for females and for more peripheral than for more central retinal eccentricities of the visual stimulus. However, the study of St John and colleagues left unaddressed the relationship between intra- and inter-subject variability in the CUD. In other words, given a group of normal subjects and a distribution of CUD values in these subjects, do reproducible intersubject differences in the CUD account for most of the distribution, or does intra-subject variability in the CUD from session to session account for the distribution of CUD values?

To address this question, three normal right-handers were tested in a series of experimental sessions of simple reaction times to lateralized flashes, for a total of 40,000 trials (16,000 trials in one subject and 12,000 trials each in the two remaining subjects). We then compared the results of these extended sessions on the same three subjects, with the results obtained on a sample of 15 normal right-handers that were tested with the same apparatus and under the same experimental conditions in one experimental session only.

2. Methods

2.1. Subjects

Three UCLA undergraduate students (JK, PB, RR) gave informed consent in accord with UCLA Human Subject Protection Committee guidelines and participated in the experiment. They were all males and right-handers as assessed by a questionnaire modified from Oldfield [20]. Subjects had a normal history, as well as normal general medical and neurological examination.

To match CUD variability in these three normal volunteers with the variability observed in a group of normal subjects, data obtained from the first 15 subjects enrolled in a previously published study [14] were used. These 15 subjects performed a task that was identical to the task performed repeatedly by the three normal volunteers tested here.

2.2. Apparatus

A Macintosh computer monitor was placed 57 cm away from subjects' eyes. A central fixation cross was presented throughout the study. Subjects had their chins in a chinrest and eyes aligned with the fixation cross on the horizontal plane. The software package MacProbe was used for stimulus presentation and response recording [26]. As in the previously published study [14], subjects used microswitches for motor responses and were presented with black flashes lasting 50 ms on a grey background and subtending one degree of visual angle at 4° from the midsagittal plane and on the horizontal plane. Stimuli were presented after a warning tone of 1000 Hz and lasted 100 ms, after a randomly varied interval from 500 to 2500 ms.

JK and RR were tested in 15 sessions, for a total of 12,000 each. PB was tested in 20 sessions, for a total of 16,000 trials. Each testing session consisted of 20 blocks of 40 experimental trials, 20 trials per visual hemifield in a random order. The use of right and left hand for motor response was alternated across blocks. The subjects' task was to respond with the index finger upon detection of the light stimulus.

2.3. Data analysis

Reaction times (RT) shorter than 150 ms were considered anticipatory responses, whereas RT longer than 500 ms were considered attentional errors. Both were removed from the analyses. Median and mean RT for each visual hemifield (left, right) and response hand (left, right) condition were computed. The CUD was calculated by subtracting the sum of the RT of the uncrossed response conditions (left hand, left visual hemifield and right hand, right visual hemifield) from the sum of the RT of the two crossed response conditions (left hand, right visual hemifield and right hand, left visual hemifield), and dividing this difference by two.

A potential problem when median RT are computed over samples of unequal size, is that medians tend to be slightly differently biased between the two samples. This, however, tends to occur only for small samples and should not affect samples of RT with over a hundred of trials [19]. Given that the CUD is computed as a difference between RT samples of identical size, this potential problem should not affect our calculations. In any case, we used both medians and means to calculate our CUDs and to compare variability in this parameter. Results were identical for both medians

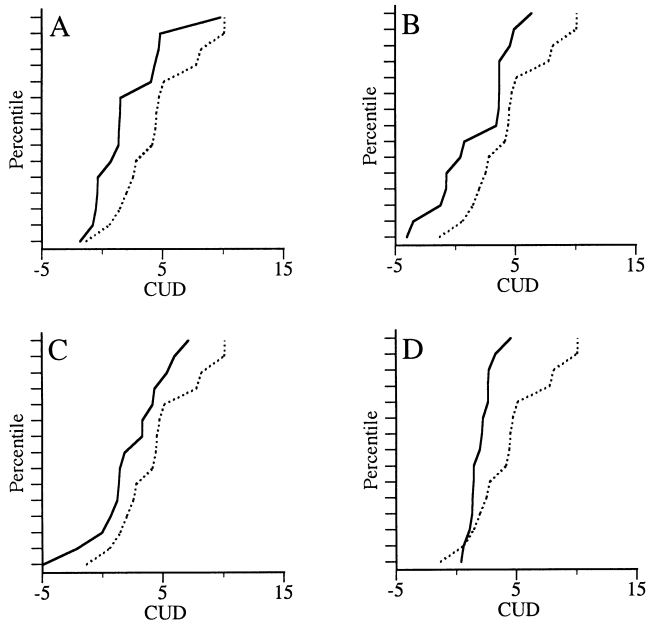

Fig. 1. Cumulative distribution functions of CUDs. The hatched line represents, in all four graphs, the CUDs of 15 normal subjects tested once. The solid line represents the CUDs obtained in JK (A), PB (B), and RR (C) in each session. There is no difference in distribution functions in (A), (B), and (C). In (D), the solid line represents the cumulative distribution function of five CUD values computed over three consecutive sessions in JK, PB, and RR. The two distribution functions in (D) are statistically different ($P < 0.03$).

and means, and only results from median RT are presented here.

To formally test the distribution of CUDs, crossed, and uncrossed responses within and between subjects, a Kolgomorov–Smirnov analysis was used.

3. Results

Subject PB was available for five testing sessions more than subjects JK and RR. The additional testing sessions in PB were analyzed, and were in agreement with the results obtained from the 15 testing sessions in all three subjects. Here, for the sake of consistency, we often present only results from the first 15 testing sessions in PB.

The grand CUD, computed over 12,000 trials, was 2 ms in JK, 1.45 ms in PB, and 2.25 ms in RR. When CUDs from each testing sessions were considered, JK had a range of CUDs from −4.02 to 6.37 ms, with five negative CUDs and a mean value of 1.67 ms, PB had a range of CUDs from −4.95 ms to 7.15 ms, with three negative CUDs and a mean value of 2.2 ms, and RR had a range of CUDs from −1.85 to 9.77 ms, with five negative CUDs and a mean value of 2.03 ms.

To formally compare the within-subject variability of CUDs in our three subjects with the between-subject variability in a group of 15 normal right handers, we used Kolgomorov–Smirnov analyses. Individual CUD distributions were not different from the CUD distribution of normal right handers (Fig. 1(A)–(C)).

We then computed the CUDs over three consecutive sessions (for a total of 2400 trials) in each subject, obtaining five CUDs per subject. When these values were considered, subject JK had a range of CUDs from 1.12 to 2.75 ms, with no negative CUDs and a mean value of 1.98 ms, subject PB had a range of CUDs from 0.4 to 3.3 ms, with no negative CUDs and a mean value of 1.58 ms, and subject RR had a range of CUDs from 1.37 ms to 4.57 ms, with no negative CUDs and a mean value of 2.46 ms. When the distribution of these values in each subject was analyzed, no differences emerged between the CUD distribution of the three subjects (Fig. 2). We then compared the cumulative distribution of these 15 CUDs estimated over three sessions in each subject with the distribution of CUDs in 15 normal volunteers tested only once (Fig. 1(D)). A significant difference ($P < 0.03$) between the two distributions was observed.[1]

Given that the CUD values of our three subjects were slightly shorter than the CUD values returned by recent meta-analyses [7,18], we tested whether the extended practice on simple RT to lateralized flashes might have affected the CUD of our three subjects. On each of our subject, however, no visible practice effects were observed on CUD over time (Fig. 3).

We subsequently ordered RT from the fastest to the

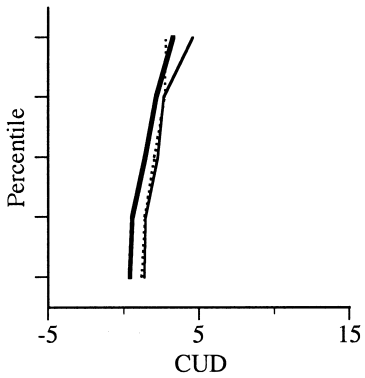

Fig. 2. Cumulative distribution functions of CUDs computed over three consecutive sessions in JK, PB, and RR. The distribution functions do not differ.

[1] We also computed the CUD over two sessions and compared the cumulative distribution of CUDs over two sessions with the distribution of CUDs in the same 15 normal volunteers tested once. To do so, we used the first 10 sessions in JK, PB and RR, obtaining five CUDs in each subject. When the cumulative distribution of these CUDs obtained over two sessions was formally compared with the cumulative distribution of CUDs in the 15 normal volunteers tested once, no differences emerged.

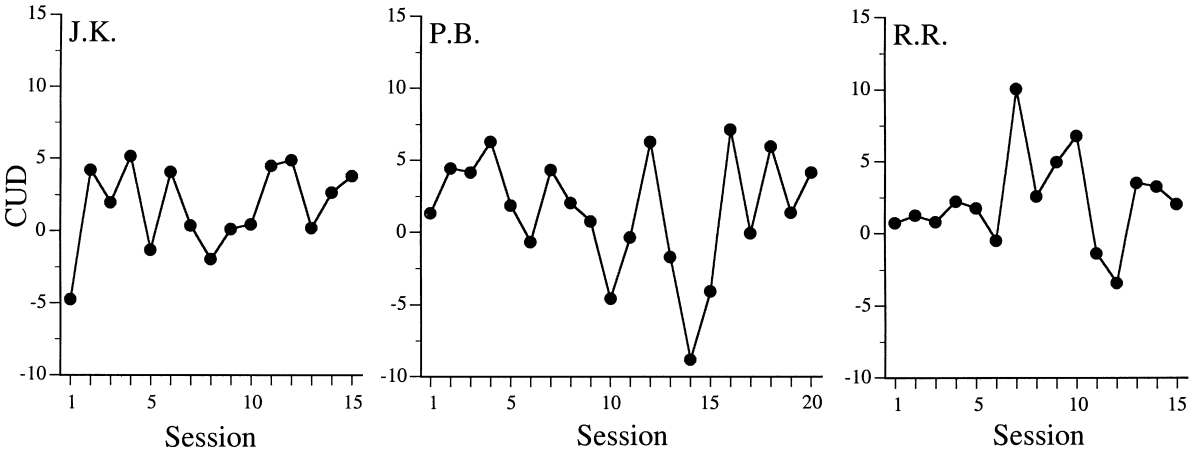

Fig. 3. CUDs in each session in each subject, in chronological order. Practice effects on the CUD are not observed.

slowest for crossed and uncrossed responses separately in each subject. We then divided the obtained distribution of RT into 10 bins and calculated the CUD in each bin, from the fastest to the slowest. A remarkably stable CUD over the entire distribution was obtained with this method (Fig. 4).

We also computed the variability for crossed and uncrossed responses separately over the 15 experimental sessions in each subject (Fig. 5). To formally compare the within-subject variability of crossed and uncrossed responses separately in our three subjects with the between-subject variability in the group of 15 normal right handers tested once, we used Kolgomorov–Smirnov analyses. Individual RT distributions for crossed and uncrossed responses were significantly different ($P < 0.05$) in all cases from the RT distributions for crossed and uncrossed responses, respectively, in the group of 15 normal right handers.

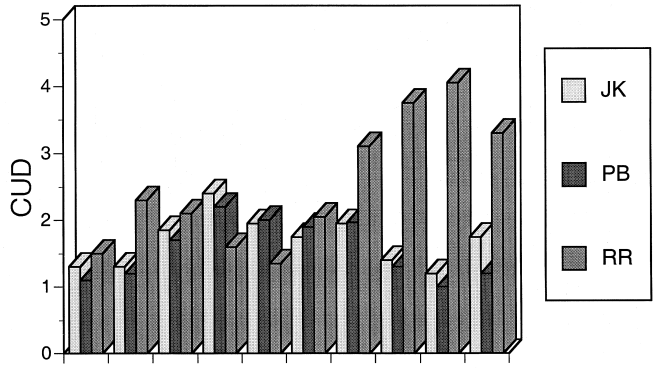

Fig. 4. CUDs computed in 10 bins of ordered RT, from the fastest to the slowest (from left to right in the graph), in the three subjects tested repeatedly. Subjects PB and JK tend to show larger CUDs in the central bins, whereas subject RR shows larger CUDs in the slowest bins. However, all CUDs are in a very small range, from 1 to 4 ms.

4. Discussion

To the best of our knowledge, the data presented here are the largest RT dataset collected in single subjects, when performing unimanual simple RT to lateralized flashes. When the CUD was estimated in the same subject in 15 different sessions, the variability of the parameter was largely similar to the variability observed in a group of 15 normal subjects tested once. This was observed in all three subjects that were repeatedly tested, as shown in Fig. 1. When the CUD was estimated, however, over larger samples of data, its variability was much reduced, not only within subjects, but also between subjects, as shown by Fig. 2. Of course, three normal volunteers do not represent a large sample of subjects, and it may be that, just by chance, we tested three subjects with similar CUD patterns. This, however, seems to us unlikely. In fact, a previous study on simple reaction times to lateralized flashes reported CUD values in large groups of subjects that were very similar to the CUD observed in our three subjects [17]. We beleive our results suggest that the variability in CUD observed in previous studies is not produced by stable individual differences but rather by session-to-session changes that can occur in the same subject. In contrast, when the variability of overall RT for crossed or uncrossed responses in the three subjects tested repeatedly was compared to the variability observed in a group of 15 normal subjects tested once, differences emerged, suggesting that overall RT for crossed and for uncrossed responses is indeed a stable intersubject difference, at variance with the CUD.

We believe that these results have both methodological and theoretical implications. Before discussing these implications, however, we have to address a methodological issue. Our three subjects were tested over sessions comprising a total of 800 trials. The 15

subjects tested once, were tested over sessions comprising a total of 560 trials. If any, this difference should bias the results toward a reduction in CUD variability in the three subjects repeatedly tested. Instead, we have seen that no difference in CUD variability within and between subjects was observed. Thus, the difference in total number of trials between sessions seems not to influence the main result of the study. At any rate, we also performed analyses including only the first 560 trials of the longer, within-subject sessions. The results were substantially identical to the results presented here. The only noticeable difference when only the first 560 trials of the longer sessions were analyzed was that PB had five negative CUDs, compared to the three negative CUDs observed when sessions were analyzed in their entirety.

From a methodological standpoint, the main implication of our findings is that to have a reproducible CUD parameter in the same subject, long experimental sessions comprising about 2000 trials should be performed. Suppose, for instance, that one is interested in measuring the CUD in a patient, or a series of patients, before and after surgical sections of callosal fibers, to test whether the presence or absence of different callosal regions have an impact on the CUD. Our data suggest that it would be prudent to perform the experiment with at least 2000 trials before and after the surgery (which is, ironically, what we did not do in a study published some years ago) [10]. Thus, to ascribe a change in the CUD of a single subject to a specific lesion in the brain, one has to be sure that changes would not occur spontaneously. For a group of subjects, however, we believe that the current tendency to run about 600–800 trials per subject is not seriously challenged by our data, as long as the sample size is large enough. In fact, assuming that spontaneous variations in the CUD unrelated to task variations may occur, a large enough size of the group of subjects enrolled in a hypothetical study should facilitate a roughly even distribution of these spontaneously occurring variations, and differences between groups may more likely represent 'true' experimental effects of, say, varying visual, attentional, or motor aspects of the task. An indirect support to this comes from our dataset. When a mean CUD value was computed from the variable CUD values of each individual session, results in each subject were not very different from the CUD computed using median RT for each visual hemifield-response hand condition of the entire dataset.

More interesting, however, seem to us the theoretical implications of our data. The large variability in the CUD observed within the same subject repeatedly tested is reminiscent of the complex ever-varying spatiotemporal dynamics observed from trial to trial with electrical scalp recordings during simple RT to lateralized flashes [22–24]. What the electrical scalp recordings data show is that even the same visuomotor condition, say left visual hemifield — right hand, may be associated with entirely different activation patterns in two different trials in the same subject. Thus, the variability observed by us in the same subject, rather than being simply interpreted as a 'nuisance' or noise that we have to try to get rid of, may actually represent the behavioral counterpart of physiological dynamics, the meaning of which is still largely to be determined. Given that these spatiotemporal patterns of activation cannot be controlled by the experimenter, the only empirical solution is to obtain very large datasets, in which it is likely that these (apparently) random fluctuations in cortical activation will be more or less evenly distributed in all the experimental conditions, thus influencing only minimally the parameter of interest, namely the CUD. In fact, when we ordered RTs from the fastest to the slowest and computed the CUD in 10 bins over the entire distribution of RT (thus, presumably 'equalizing' different patterns of cortical activation for crossed and uncrossed responses

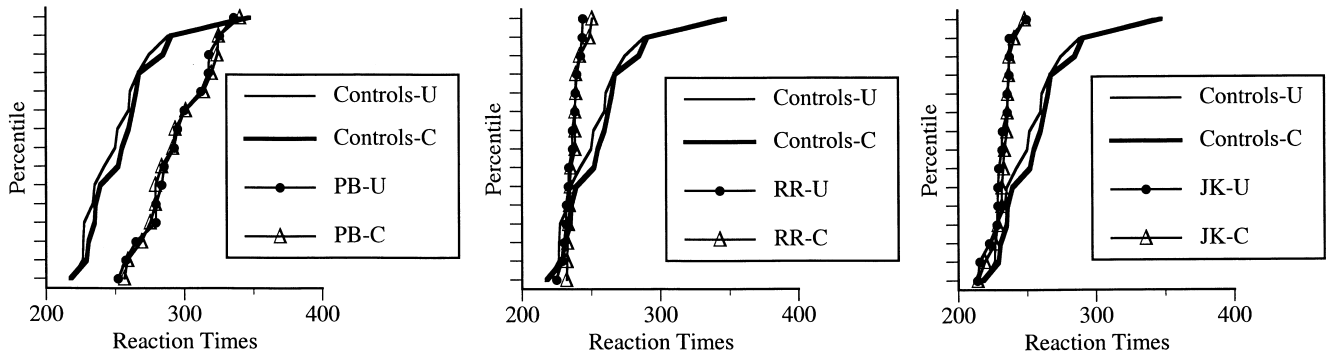

Fig. 5. Distribution of RT for crossed and uncrossed responses in the three subjects tested repeatedly and in the 15 subjects tested once. The distributions obtained in a single subject are always statistically different (Kolgomorov–Smirnov, $P < 0.05$). Subject PBs distribution, however, is less strikingly different from the distribution obtained in the group of 15 subjects tested once than subjects JK and RRs distributions.

that are generally associated with response speed, see Saron et al. [23]), we obtained a very stable CUD.

Empirical evidence in favor of both the hard-wired (callosal relay) and the functional (hemispheric activation) model of the CUD have been provided [2,9,22,24]. It seems to us that our data may be more easily explained by the hard-wired model. Our hypothesis is that the CUD represents the conduction delay through callosal fibers that must occur, *all the other things being equal*, for crossed but not for uncrossed responses. Given the short delay, the only callosal fibers that could mediate this delay, assuming that callosal fibers have conduction velocities similar to the ones observed in the peripheral nervous system and correlated with diameter and myelination, would be large diameter myelinated fibers operating at fast conduction velocity [5]. Such fibers can be observed in the human corpus callosum grouped in two contingents, one in the midbody, and the other one in the tip of the splenium [1].

The very stable CUD obtained in all bins over the entire distribution of RTs, it seems to us, cannot be readily explained by functional mechanisms of unbalanced hemispheric activation [15,16]. These mechanisms are likely characterized, as most functional mechanisms, such as priming effects, inhibition of return and the like, by specific time-courses, with increasing strength of the effect up to a given point in time, then decreasing strength of the effect thereafter. This is likely to generate different CUDs over the whole distribution of RT. In particular, if we correctly interpret Kinsbourne's model, it should predict larger CUDs for the fastest RT. It must be said, however, that the time window under scrutiny here is extremely narrow (from 140 to 500 ms after stimulus onset). Although this corresponds to the typical time course of automatic lexical priming effect, we cannot rule out the possibility that the CUD may reflect functional mechanisms that persist over this narrow time window.

The bins analysis of the CUD has returned very short CUD values. This is in contrast with electrical scalp recordings of the CUD, in which when quartiles analyses were performed, much longer CUD estimates were obtained over the entire distribution [22,24]. The discrepancy between behavioral and electrical scalp recordings estimates of the CUD is puzzling and our experiment was not designed to clarify this issue. It must be noted, however, that when in-depth electrodes were used to estimate the CUD in epileptic patients, these neurophysiological estimates were much more similar to behavioral estimates than the ones obtained with electrical scalp recording techniques (Jeff Clarke, personal communication).

The CUD observed in our three subjects tested repeatedly is somewhat shorter than the CUD documented by a recent meta-analysis [18]. We cannot exclude the possibility that our three subjects tested over several thousands of trials have a particularly short CUD or are peculiar in some other way (e.g., motivation). In fact, our group of 15 subjects has a mean CUD that closely corresponds to the values of Marzi's meta-analysis [18]. We can exclude, however, the possibility that the CUD gets shorter with practice. In fact, we tested this hypothesis analyzing the CUDs progressively over time in each of our three subjects, and no practice effects were observed.

To conclude, our data suggest that: (i) it is possible to minimize CUD variability in simple RT to lateralized flashes using prolonged testing sessions (the number of trials that stabilized the CUD in our subjects is 2400); (ii) within- and between-subject variability in the CUD are likely produced by the same complex visuomotor dynamics; and (iii) when these complex visuomotor dynamics are subtracted out, what remains is a fast, hard-wired mechanism of transfer through the corpus callosum that generates the CUD.

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References

[1] Aboitiz F, Scheibel A, Fisher R, Zaidel E. Fiber composition of the human corpus callosum. Brain Research 1992;598:143–53.
[2] Aglioti S, Berlucchi G, Pallini R, Rossi GF, Tassinari G. Hemispheric control of unilateral and bilateral responses to lateralized light stimuli after callosotomy and in callosal agenesis. Exp Brain Research 1993;95:151–65.
[3] Anzola GP, Bertoloni G, Buchtel HA, Rizzolatti G. Spatial compatibility and anatomical factors in simple and choice reaction time. Neuropsychologia 1977;15:295–302.
[4] Bashore TR. Vocal and manual reaction time estimates of interhemispheric transmission time. Psychological Bulletin 1981;89:352–68.
[5] Berlucchi G. Interhemispheric integration of simple visuomotor responses. In: Buser A, Rougeul-Buser D, editors. Cerebral correlates of conscious experience. Amsterdam: Elsevier, 1978. p. 83–94.
[6] Berlucchi G, Heron W, Hyman R, Rizzolatti G, Umiltá C. Simple reaction times of ipsilateral and contralateral hand to lateralized visual stimuli. Brain 1971;94:419–30.
[7] Braun CM. Estimation of interhemispheric dynamics from simple unimanual reaction time to extrafoveal stimuli. Neuropsychological Review 1992;3:321–65.
[8] Clarke J, Zaidel E. Simple reaction times to lateralized flashes: varieties of interhemispheric communication routes. Brain 1989;112:849–70.
[9] Di Stefano M, Morelli M, Marzi CA, Berlucchi G. Hemispheric control of unilateral and bilateral movements of proximal and distal parts of the arm as inferred from simple reaction time to

lateralized light stimuli in man. Exp Brain Research 1980;38:197–204.
[10] Iacoboni M, Fried I, Zaidel E. Callosal transmission time before and after partial commissurotomy. NeuroReport 1994;5:2521–4.
[11] Iacoboni M, Woods RP, Lenzi GL, Mazziotta JC. Merging of oculomotor and somatomotor space coding in the human right precentral gyrus. Brain 1997;120:1635–45.
[12] Iacoboni M, Woods RP, Mazziotta JC. Brain-behavior relationships: evidence from practice effects in spatial stimulus-response compatibility. Journal of Neurophysiology 1996;76:321–31.
[13] Iacoboni M, Woods RP, Mazziotta JC. Bimodal (auditory and visual) left frontoparietal circuitry for sensorimotor integration and sensorimotor learning. Brain 1998;121:2135–43.
[14] Iacoboni M, Zaidel E. Channels of the corpus callosum: evidence from simple reaction times to lateralized flashes in the normal and the split brain. Brain 1995;118:779–88.
[15] Kinsbourne M. The corpus callosum equilibrates hemispheric activation. In: Zaidel E, Iacoboni M, editors. The parallel brain: the cognitive neuroscience of the corpus callosum. Cambridge, MA: MIT Press, 2000 [in press].
[16] Ledlow A, Swanson JM, Kinsbourne M. Differences in reaction times and average evoked potentials as a function of direct and indirect neural pathways. Annals of Neurology 1978;3:525–30.
[17] Levy J, Wagner N. Handwriting posture, visuomotor integration, and lateralized reaction-time parameters. Human Neurobiology 1984;3:157–61.
[18] Marzi CA, Bisiacchi P, Nicoletti R. Is interhemispheric transfer of visuomotor information asymmetric? Evidence from a meta-analysis. Neuropsychologia 1991;29:1163–77.
[19] Miller J. A warning about median reaction time. Journal of Experimental Psychology: Human Perception and Performance 1988;14:539–43.
[20] Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9:97–113.
[21] Poffenberger A. Reaction time to retinal stimulation with special reference to the time lost in conduction through nervous centers. Archives of Psychology 1912;23:1–73.
[22] Saron C, Vaughan HG, Simpson G, Foxe JJ. Timing and spatial distribution of interhemispheric visuomotor communication. Human Brain Mapping 1995;2(Suppl. 1):289.
[23] Saron CD, Vaughan HG, Foxe JJ, Simpson GV. Multiple visuomotor activation and motor output pathways in simple RT. NeuroImage 1998;7:S960.
[24] Saron CD, Vaughan HG, Foxe JJ, Simpson GV. Electrophysiological indices of intra- and interhemispheric visuomotor interaction. In: Zaidel E, Iacoboni M, editors. The parallel brain: the cognitive neuroscience of the corpus callosum. Cambridge, MA: MIT Press, 2000 [in press].
[25] St John R, Shields C, Krahn P, Timney B. The reliability of estimates of interhemispheric transmission times derived from unimanual and verbal response latencies. Human Neurobiology 1987;6:195–202.
[26] Zaidel E, Iacoboni M. Using a computerized system for behavioral laterality experiments. Brain 1996;119:2155–6.