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ORIGINAL ARTICLE

Multisensory integration and behavioral stability

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Abstract

Information coming from multiple senses, as compared to a single one, typically enhances our performance. The multisensory improvement has been extensively examined in perception studies, as well as in tasks involving a motor response like a simple reaction time. However, how this effect extends to more complex behavior, typically involving the coordination of movements, such as bimanual coordination or walking, is still unclear. A critical element in achieving motor coordination in complex behavior is its stability. Reaching a stable state in the coordination pattern allows to sustain complex behavior over time (e.g., without interruption or negative consequences, like falling). This study focuses on the relation between stability in the coordination of movement patterns, like walking, and multisensory improvement. Participants walk with unimodal and audio-tactile metronomes presented either at their preferred rate or at a slower walking rate, the instruction being to synchronize their steps to the metronomes. Walking at a slower rate makes gait more variable than walking at the preferred rate. Interestingly however, the multimodal stimuli enhance the stability of motor coordination but only in the slower condition. Thus, the reduced stability of the coordination pattern (at a slower gait rate) prompts the sensorimotor system to capitalize on multimodal stimulation. These findings provide evidence of a new link between multisensory improvement and behavioral stability, in the context of ecological sensorimotor task.

Introduction

Our ability to integrate information coming from different senses is crucial in everyday life. Multisensory improvement refers to situations where the multimodal presentation of the stimuli (i.e., via more than one sensory modality) enhances performance in comparison with unimodal stimulus presentation. To successfully integrate multimodal stimuli, three principles are particularly important: temporal coherence, spatial coherence, and inverse effectiveness (Stein & Meredith, 1993; Stein & Stanford, 2008). Temporal and spatial principles state that sensory inputs coming from different modalities have to be presented in the same spatial location (Meredith & Stein, 1986) and at the same time (Meredith, Nemitz, & Stein, 1987). According to the inverse effectiveness principle multisensory improvement is inversely related to the effectiveness of each sensory modality (Stein & Meredith, 1993). Once the three main rules are fulfilled, multisensory improvement is a common phenomenon. It has been reported using perceptual judgements, localization (Ernst & Banks, 2002; Lovelace, Stein, & Wallace, 2003; Nelson et al., 1998), and reaction time tasks (Colonius & Diederich, 2004; Hershenson, 1962; Murray et al., 2005). Although it is vital to quickly detect events and react to them, daily action does not often imply perception followed by movement in a sequential way. Many complex actions in an ecological context involve concomitant and continuous perception and movement, such as writing, speaking, or walking (Ernst & Bülthoff, 2004; Kelso, 1995). The mechanisms underlying the beneficial effect of multimodal stimuli on reaction times or on judgement tasks are well described (Rowland, Quessy, Stanford, & Stein, 2007). In contrast, evidence is less clear for continuous movement. At the neural level, multisensory neurons fire more when they are excited by several sensory signals (Stein & Meredith, 1993; Stein & Stanford, 2008) as compared to one single signal. The increase of neural firing leads to a faster detection of multimodal signals than

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unimodal signals, implying also faster neural processing (Rowland et al., 2007). Enhancing processing speed at the neuronal level has noticeable effects on behavior, noticeable in temporal judgement tasks or in reaction time tasks (Colonius & Diederich, 2004; Murray et al., 2005; Vroomen & Keetels, 2010). However, in continuous and coordinated actions, even though speeding reaction time to changes is relevant, other properties of behavior matter, notably the stability of the coordination pattern (Bruijn, Meijer, Beek, & Dieën, 2013; Kelso, Fink, DeLaplain, & Carson, 2001; Repp & Su, 2013). Indeed, continuous behavior requires the movements' coordination of several body parts, or/and with the surroundings. This coordination involves reaching a stable state, which ensures the formation and persistence of behavioral patterns, in time and space. These continuous behaviors are allowed by the capacity of the sensorimotor system to resist unexpected changes or events, such as the fast recovery of the intended behavioral pattern after a perturbation (for an introduction, see Kelso, 1995). This general property of behavioral patterns refers to the concept of stability (Haken, Kelso, & Bunz, 1985; for a mathematical introduction see Strogatz 2018), and is determined by cognitive, perceptual, and motor processes (Bressler & Kelso, 2001; Huys, Perdikis, & Jirsa, 2014; Large & Jones, 1999; Warren, 2006). The theoretical framework upon which the present study is based is coordination dynamics (Kelso, 1995). This approach exploits dynamical systems modeling to understand how behavioral patterns emerge and change over time and has been applied to the study of multisensory processes (Lagarde & Kelso, 2006; Lagarde, Zelic, & Mottet, 2012; Zelic, Mottet, & Lagarde, 2012, 2016; Roy, Lagarde, Dotov, & Dalla Bella, 2017; Roy, Dalla Bella, & Lagarde, 2017). The theoretical framework accounts for the consequences of biological noise pervasive in the nervous system (Schöner et al., 1986; Schöner & Kelso, 1988). For rhythmic actions, the approach is based on mathematical models of coupled oscillators and of forced oscillators (Haken et al., 1985; Schöner & Kelso, 1988), in which the perception of periodic events affects the behavior of a movement oscillator generator leading to entrainment and synchronization, and thus to increased temporal stability. For example, when we walk in a crowded street we can all keep walking even if someone nudges and touches us. When the step rate is manipulated, the stability of gait varies between very stable and barely stable (Bruijn, van Dieën, Meijer, & Beek, 2009; Dingwell & Marin, 2006; Jordan, Challis, & Newell, 2007; Terrier & Dériaz, 2012; Yamasaki, Sasaki, Tsuzuki, & Torii, 1984). When walking in a crowd, stable gait tremendously reduces the risk of falling.

In this study, gait was chosen as a representative case of continuous action. Moreover, continuous actions often possess a rhythmic character. A classical paradigm to study the effect of sensory stimuli on continuous behavior is the sensorimotor synchronization task. It consists in synchronizing movements such as finger/hand taps or steps while walking to the beats of a metronome or music (Repp, 2005; Repp & Su, 2013). As previous studies have shown that the stability of motor behavior can be directly quantified in sensorimotor synchronization (Schöner, Haken, & Kelso, 1986; Kelso, 1995; Warren, 2006), this task appears as ideal to assess the effect of stability on multisensory integration. Walking to the beat of a metronome can be assessed by (1) the stability of the behavior and (2) the ability to synchronize with the timekeeper, for example a metronome. Gait stability is commonly measured by calculating the variability of the coordination between the feet (Bruijn et al., 2009; based on the framework proposed in: Schöner et al., 1986). It is well known and widely applied across disciplines that varying the stability of a noisy dynamical system has a systematic effect onto the standard deviation of its distribution; therefore, standard deviation provides a straightforward quantification of stability (Dakos et al., 2012; Gardiner, 2003). In the same line, the ability to synchronize is measured by the variability of the time between the onset of the stimuli and the movement, which is equivalent to the variability of the relative phase between stimuli and movement. Continuous behaviors are characterized by two types of variables: behavior stability and stimuli synchronization.

A puzzling result often reported in the literature is that both variables are not similarly influenced by multimodal stimuli. When considering synchronization in finger tapping, stepping, or swinging wrist-pendulum tasks, multisensory improvement is found when the sensory properties of the stimuli are manipulated (presenting the stimuli continuously: Armstrong & Issartel, 2014; Varlet et al., 2012, or decreasing the reliability of one of the modality: Elliott, Wing, & Welchman, 2010, 2011; Wright & Elliott, 2014). Multisensory improvement, however, is not consistently reported (Ammirante, Patel, & Russo, 2016; Lagarde & Kelso, 2006; Lagarde, Zelic, & Mottet, 2012; Zelic, Mottet, & Lagarde, 2016). When considering the stability of the behavior, multisensory improvement was found in two previous studies assessing bimanual-finger and juggling coordination (Zelic, Mottet, & Lagarde, 2012, 2016). Yet, as found for synchronization variables, multisensory improvement was not consistently found across various tasks, such as bimanual coordination (Blais, Albaret, & Tallet, 2015; Blais, Martin, Albaret, & Tallet, 2014; Lagarde et al., 2012; Zelic et al., 2016), stepping (Wright & Elliott, 2014), or gait (Roy et al., 2017b; Sejdić et al., 2012). However, both studies showing a benefit of multimodal stimulation on coordination (Zelic, Mottet, & Lagarde, 2012, 2016) tested bimanual coordination. Interestingly, multimodal stimulation improved stability particularly for the least stable bimanual coordination pattern, i.e., moving in antiphase (Zelic et al., 2016). This points to a relation between the intrinsic behavioral stability of the action and the benefit of multimodal stimulation.

Eventually, literature reports in most cases a multisensory improvement in the ability to synchronize but not in the stability of the behavior. Consequently, the underlying mechanisms for both variables might be different. On one hand, speeding up signal processing via multimodal stimuli may improve synchronization performances. On the other hand, multimodal stimuli do not influence behavior stability, except when the coordination pattern between both hands is the least stable (Zelic et al., 2016). The intrinsic behavioral stability seems to be the variable of interest which allows the beneficial effect of multimodal stimuli. The current study aims at confirming the hypothesis of the changing influence of multimodal information when the coordination pattern becomes less stable. A possibility is that the sensorimotor system will become more sensitive to its surrounding environment by counterbalancing its own loss of stability, e.g., capitalizing more on multimodal stimuli. To summarize our hypothesis, we predict that the effect of multisensory integration on behavior is controlled by the current stability of the underlying coordinated movement.

To test this hypothesis, we contrast two conditions involving multisensory integration during walking: one in a condition of stability of the motor pattern and the other in a condition of poor stability. Participants walked with audio-tactile metronomes presented at their preferred walking rhythm in one condition and at a significantly slower rhythm in another condition. Departure from the preferred walking rhythm makes gait less stable, as shown by higher motor variability (Bruijn et al., 2009; Dingwell & Marin, 2006; Terrier & Dériaz, 2012). We expect this decrease of stability to be accompanied by a benefit due to multimodal stimuli. In addition to the manipulation of gait stability, we varied the temporal gap between multimodal stimuli, which is known to systematically affect synchronization behavior (Roy et al., 2017a, b). The aim of manipulating the time gap is twofold: first, to make sure we test the optimal configuration of audio-tactile stimuli, and second, to verify that multimodal stimuli were not neglected in one or the other rate condition, i.e., the effect of multimodal stimuli time alignment should be comparable in the stable and less stable gait conditions.

Method

Seventeen students (7 females) from the University of Montpellier participated in the study. Three participants were excluded, because they were poor synchronizers, as they departed by more than 2 SD from the group average (as in Sowiński & Dalla Bella, 2013). In addition, across participants, trials showing very poor synchronization (8 out of 196) were discarded. Sample size necessary to detect an effect (power = .8; alpha of .05 as suggested by Cohen, 1988; $n = 14$) was determined after running a power analysis based on data from a similar experiment (Roy et al., 2017b, Cohen's $d = .70$). Participants were equipped with earphones and vibrators—on their index fingers—delivering auditory and tactile stimuli and were instructed to walk around an indoor round path (walkway width = 3.5 m; length = 6.7 m; see Fig. 1). First, we recorded the participants' preferred walking rate by asking them to walk for 1 min at their most comfortable rate. In a second phase, participants were instructed to synchronize their heel strikes to the metronomes. All conditions were performed (1) with a stimulus rate corresponding to each participant's preferred rate (average step time = 566.48 ms, SD = 45.86), and (2) with a slower stimulus rate (by 30% relative to their preferred rate; average step time = 736.4 ms, SD = 59.61). Participants walked with a tactile metronome and with an auditory metronome in two separate unimodal conditions. In addition, they walked with an audio-tactile metronome, with the instruction to synchronize their heel strikes to the tactile stimuli (Roy et al., 2017b). In five multimodal conditions, the temporal gap between tactile and auditory stimuli was manipulated. Stimuli from the two modalities were either synchronous (temporal gap = 0) or non-synchronous

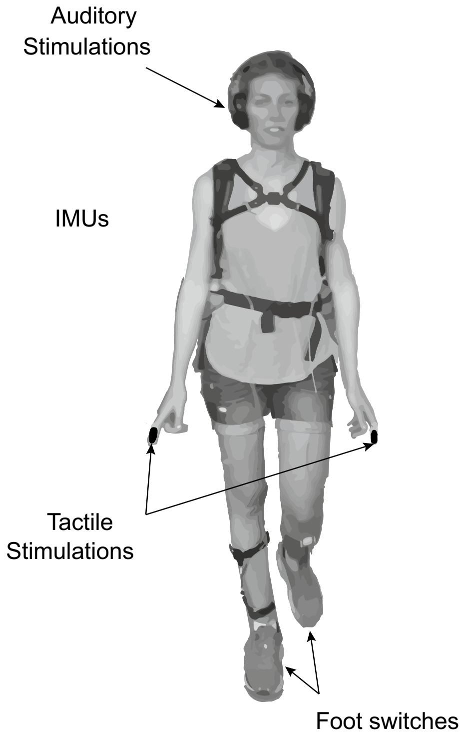

Fig. 1 Two tactile vibrators were positioned on the participants' index fingers. Auditory stimuli were delivered via earphones. In addition, participants wore silent headphones to reduce environmental noise. To record steps' intervals and asynchronies, participants were equipped with IMUs (Inertial Measurement Unit) and foot switches

(temporal gap = − 120, − 40, 40 and 120 ms). When stimuli were non-synchronous, tactile stimuli occurred either before (positive gap) or after auditory stimuli (negative gap). There were 14 conditions: 7 (2 unimodal and 5 multimodal) × 2 rates. Footfall times were recorded via foot switches positioned on the participants' shoe soles.

Behavioral stability can be quantified by measuring the variability of steady rhythmic behavior (Kelso, 1995). One can use the standard deviation of a series of successive temporal intervals between movements and stimuli, and/or between two consecutives movements (e.g., fingers taps or steps in gait). Therefore, step times between two consecutive footfalls were measured to quantify gait variability. A motor score was obtained by computing the Coefficient of Variation of step times $[(\mathrm{SD}_{\text{step time}}/\mathrm{Mean}_{\text{step time}}) \times 100]$ expressed in percentage (see Fig. 2a). The motor score was obtained by taking the average of the coefficient of variation obtained for left–right steps and for right–left steps. A large score reflected variable gait, which is interpreted as a less stable gait, and consequently as a poor performance (Bruijn, Meijer, Beek, & Dieën, 2013). We calculated a difference motor score to test the presence of multisensory improvement at the different gaps (see Fig. 2a). The difference motor score was obtained by subtracting participants' motor score in the unimodal tactile condition from the motor score in the multimodal conditions.

Temporal differences between footfalls and tactile stimuli were measured to quantify synchronization abilities. A synchronization score was calculated, corresponding to the Coefficient of Variation of the time differences between steps and tactile stimuli $[\mathrm{SD}_{\text{step-stimuli}}/\mathrm{Mean}_{\text{stimuli-stimuli}} \times 100]$ expressed in percentage (see Fig. 3a). A larger score indicated a poorer synchronization (Sowiński & Dalla Bella, 2013). We calculated a difference synchronization score to test the presence of multisensory improvement at the different gaps (see Fig. 3a). The difference synchronization score was obtained by subtracting participants' synchronization score in the unimodal tactile condition from the synchronization score in the multimodal conditions.

Results

Walking at a slower rate degraded the performance, as it made gait more variable (see Fig. 2a). A significantly higher motor score was found across temporal gaps at the slower rate than at the preferred rate, as revealed by a 2 (rates) × 5 (temporal gaps) two-way ANOVA ($F(1117) = 5.96$, $p < .01$, $\eta^2 = .05$). The two-way ANOVA also showed that there was no significant rate × temporal gap interaction ($F(4117) = .57$, $p = .68$, $\eta^2 = .02$), but an effect of the temporal gap ($F(4117) = 2.99$, $p = .05$, $\eta^2 = .1$). A multisensory improvement was apparent only when participants walked at the slower rate (see Fig. 2b). Difference motor score in multimodal conditions was lower than the zero baseline only for the slower rate [gap = 0 ms, $t(13) = -3.59$, $p = .003$, $d = .96$;

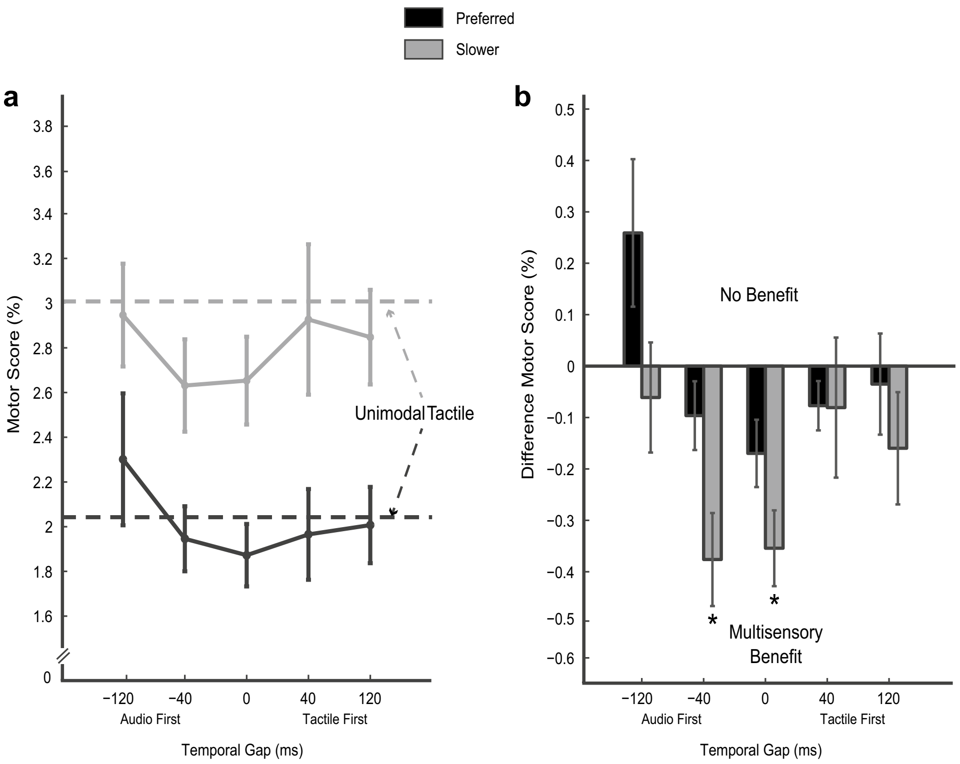

Fig. 2 Motor score (%), indicating variability of steps times for preferred (black) and slower (gray) walking rates, as a function of the five temporal gaps. Means for the unimodal tactile conditions are indicated by dotted lines. **a** Degraded gait performance for the slower rate. **b** Multisensory improvement selectively for the slower rate. Error bars indicate SE of the Mean. Stars indicate significant differences from the baseline (difference motor score = 0)

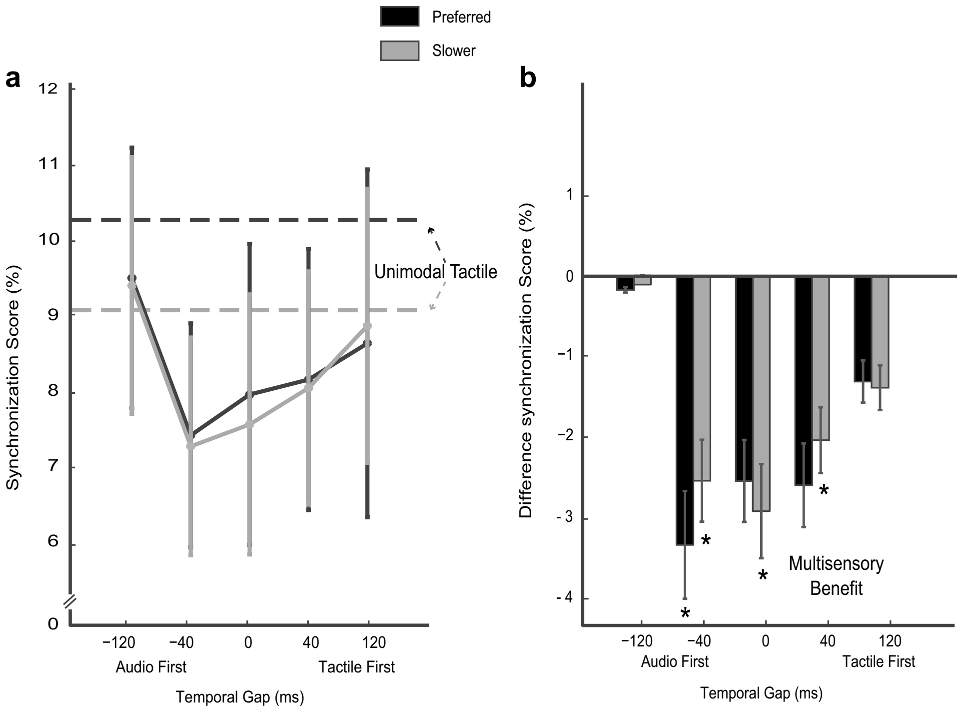

Fig. 3 Synchronization score (%) indicates synchronization performance for preferred (black) and slower (gray) walking rates, as a function of the five temporal gaps. Means for the unimodal tactile conditions are indicated by dotted lines. **a** Similar synchronization performance for both rates. **b** Multisensory improvement for both rates. Error bars indicate SE of the Mean. Stars indicate significant differences from the baseline (difference synchronization score = 0)

gap = − 40 ms, $t(13) = -3.11$, $p = .005$, $d = .83$; Bonferroni corrected $p < .005$]. At a slower rate, none of the three other gaps were significantly different from the zero baseline [gap = − 120 ms, $t(13) = -1.09$, $p = .29$; gap = 40 ms, $t(13) = -.44$, $p = .66$; gap = 120 ms, $t(13) = -1.10$, $p = .29$], neither were all the gaps at the preferred rate [gap = − 120 ms, $t(13) = 1.35$, $p = .20$; gap = − 40 ms, $t(13) = -1.08$, $p = .30$; gap = 0 ms, $t(13) = -1.94$, $p = .07$; gap = 40 ms, $t(13) = -1.20$, $p = .25$; gap = 120 ms, $t(13) = -.27$, $p = .79$].

Slowing down the walking rate relative to the preferred rate did not affect synchronization (see Fig. 3a). A 2 (rate) × 5 (temporal gaps) two-way ANOVA showed that the synchronization score did not change when participants departed from their preferred rate ($F(1,97) = .19$, $p = .66$, $\eta^2 = .03$). The two-way ANOVA also showed that there was no significant rate × temporal gap interaction ($F(4,97) = .19$, $p = .94$, $\eta^2 = .01$), but an effect of the temporal gap ($F(4,97) = 4.43$, $p = .002$, $\eta^2 = .16$). The difference synchronization score (see Fig. 3b) in multimodal conditions was lower than the zero baseline for the slower rate [gap = 0 ms, $t(11) = -7.23$, $p < .001$, $d = 2.09$; gap = − 40 ms, $t(11) = -5.56$, $p < .001$, $d = 1.61$; gap = 40 ms, $t(11) = -3.90$, $p = .002$, $d = 1.13$; Bonferroni corrected $p < .005$)] and for the preferred rate [gap = − 40 ms, $t(11) = -4.24$, $p < .001$, $d = 1.22$; Bonferroni corrected $p < .005$]. At a slower rate, the two other gaps were not significantly different from the zero baseline [(gap = − 120 ms, $t(11) = .006$, $p = .99$; gap = 120 ms, $t(11) = -1.37$, $p = .19$], and also for the four other gaps at the preferred rate [gap = − 120 ms, $t(10) = -.14$, $p = .89$; gap = 0 ms, $t(11) = -2.01$, $p = .07$; gap = 40 ms, $t(11) = -2.37$, $p = .04$; gap = 120 ms, $t(11) = -.90$, $p = .38$].

Regarding the difference between the unimodal conditions: for the motor score, a 2 (rate) × 2 (modality auditory and tactile) two-way ANOVA showed that the unimodal auditory condition lead to a better performance than unimodal tactile condition [$F(1,55) = 4.22$, $p = .044$, $\eta^2 = .025$], and that the preferred rate leads to a better performance than the slower rate [$F(1,55) = 54.21$, $p < .00$, $\eta^2 = .33$]. The interaction did not reach significance [$F(1,55) = .38$, $p = .54$]. Regarding the synchronization score, a 2 (rate) × 2 (modality auditory and tactile), two-way ANOVA showed that the unimodal auditory condition led to better performance than the unimodal tactile condition [$F(1,55) = 6.23$, $p = .01$, $\eta^2 = .05$]. However, no difference between preferred and slower rates was found [$F(1,55) = .09$, $p = .75$], and no interaction [$F(1,55) = 1.43$, $p = .24$] .

Discussion

We investigate the influence of multisensory integration and behavioral stability on the gait by asking young adults to walk with audio-tactile stimuli presented at their preferred walking rate (stable behavior), or at a significantly slower rate (less stable behavior). As expected, we find that multimodal stimuli increase the stability of synchronization on both conditions of behavioral stability (i.e., preferred and slower). In contrast, multimodal stimuli selectively increase the stability of the coordination depending on the intrinsic behavioral stability of gait. Multisensory improvement is only found in the condition with poor stability (i.e., slower gait rate), while no effect is observed in stable conditions (i.e., preferred gait rate). This finding is in keeping with the hypothesis that multisensory improvement is related to gait stability. Thus, the effect of multisensory integration is scaled by the current state of behavior (stable vs. unstable). When the gait pattern is unstable, participants use multimodal information effectively improving thus their performance; in contrast, stable behavior is not conducive to using external information; therefore, the sensorimotor system does not benefit from multimodal stimuli.

To the best of our knowledge, this is first evidence that multimodal stimuli can be used for increasing the stability of gait coordination. These findings suggest that motor coordination might be more resistant to changes than synchronization. Only when the behavior becomes less stable is sensitivity to the surrounding multisensory environment significantly scaled-up. Hence, to better understand the role played by multisensory integration in everyday behavior, such as walking in a complex multisensory environment, it is important to consider the intrinsic stability of behavior. This new insight on multisensory integration may partly explain the previous contradictory findings about a multisensory benefit on motor variables (Blais et al., 2015; 2014; Lagarde et al., 2012; Zelic et al., 2016; Sejdić et al., 2012; Wright & Elliott, 2014). Indeed, we confirm that when moving at a comfortable and stable state (i.e., preferred rate,), multimodal stimuli increase the stability of synchronization but not of motor coordination. However, this effect is mediated by movement rate, relative to preferred rate. A lower rate by hindering stability favors a multisensory benefit in both synchronization and motor coordination. This last result is in keeping with our hypothesis: reducing stability increases the sensitivity of the sensorimotor system to external multimodal stimuli.

We propose to interpret the main finding of this study in the light of the inverse effectiveness principle. Accordingly, multisensory integration is maximally effective when the responses to the unimodal constituents are weak (Giard & Peronnet, 1999; Stein & Meredith, 1993). This phenomenon has been described in populations with health conditions such as brain lesion, visual, or auditory deficits (Bolognini, et al., 2013; Frassinetti, et al., 2005). Patients with these deficits benefit from audio–visual information more than healthy adults. This principle has also been reported for adults with peripheral disorders, such as short-sightedness. A concurrent sound (unrelated to the visual task to perform) improves the threshold for visual detection only in the group of participants exhibiting the poorest performance in a visual-only condition (Caclin et al., 2011). This principle has been extended to the healthy population by manipulating the task difficulty. For example, Albouy et al. (2015) reported that the multisensory improvement is greater as task difficulty increases. The current study extends this principle to the stability of behavior. Hence, the logic of the inverse effectiveness principle is not confined to multisensory integration processes, but pinpoints a broader principle. We show that in case of reduced stability, the sensorimotor system is intrinsically more sensitive or able to scale up the effect of the multimodal stimuli, for the sake of improving gait stability. This may indicate that one important function of cognitive and sensorimotor systems would be to maintain a stable behavioral state (Bressler & Kelso, 2001).

Besides the main contribution, the manipulation of temporal gaps is in line with previous literature and with our hypotheses. At preferred and slower rates, temporal gaps increase the variability of the motor coordination and of the synchronization (i.e., decrease the stability) particularly for the highest temporal gaps when the auditory stimuli were presented before the tactile stimuli (i.e., − 120 ms). This result is consistent with a well-known effect of auditory capture (Repp & Penel, 2002, 2004; Roy, et al., 2017a, b). However, we hypothesize that motor variables should not be influenced by external stimuli in case of a stable coordination pattern, i.e., preferred rate. Accordingly, no effect of the temporal gap on motor variables at a preferred rate was expected. However, that temporal gaps should influence the stability of the coordination at a preferred rate may result from a difference between improvement and alteration. These two effects are not necessarily symmetric; in principle with the same manipulation, it is possible to alter a behavior but not to improve it. Indeed, it seems possible to alter the coordination of a stable behavior via multimodal stimuli, but not to improve it. It may be more difficult to improve a stable behavior than to alter it, as there is no necessity.

Moreover, it can be noted that we report a multisensory enhancement only when the baseline is the tactile-only condition. Indeed, the auditory-only condition always leads to the best performance in terms of motor and synchronization scores. This result refers again to the effect of auditory capture, highlighting the particular link between auditory rhythmic stimuli and movement (Aschersleben & Bertelson, 2003; Kato & Konishi, 2006; Repp & Penel, 2002, 2004; Dalla Bella, 2018). To avoid a ceiling effect, i.e., auditory stimuli leading to the best performances, an effect previously reported in a bimanual synchronization task (Roy et al., 2017a, b), we chose to focus on the synchronization to the tactile stimuli, which seemed to be the most sensitive condition to audio-tactile stimulation. Moreover, our finding that multisensory improvement is maximal when the multimodal stimuli are presented simultaneously (gap = 0 ms) or close to the simultaneity (i.e., auditory stimuli presented 40 ms before the tactile stimuli) supports the temporal coherence principle, already reported for tapping and bimanual coordination tasks (Repp & Penel, 2002, 2004; Roy et al., 2017a,

b) and also for gait (Roy et al., 2017a, b). Our results report a comparable synchronization response to the time gap between stimuli in stable and less stable conditions.

To conclude, our findings confirm some well-known effects, as auditory capture, multisensory improvement on the ability to synchronize with stimulation, as well as uncover a new interesting link between multisensory improvement and behavioral stability, in the context of ecological sensorimotor task.

Compliance with ethical standards

Conflict of interest The authors Charlotte Roy, Simone Dalla Bella, Simon Pla, and Julien Lagarde declare that they have not conflict of interest.

Ethical approval The study was in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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