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ORIGINAL REPORT

POTENTIAL APPLICATION OF CROSS-MODAL STIMULATION FOR NEUROREHABILITATION: THE RELATEDNESS OF PERFORMANCE ON TASKS MEASURING COGNITIVE PROCESSES SUBSERVED BY SIMILAR PREFRONTAL SUBSTRATES

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Objective: **Rehabilitating people with prefrontal functional impairment has always been challenging. This study examined whether there are functional relationships between prefrontal processes subserved by similar neural regions. The aim was to shed light on the therapeutic potential of training one function to effect changes in another function, a phenomenon called cross-modal stimulation in neurorehabilitation. The study examined risky decision-making by people of high or low odour-identification ability because both processes are subserved by the orbitofrontal regions.**

Method: **This question was examined in a sample of women ($n = 44$) with high or low odour-identification ability, classified according to their performance on the Odour Identification Test. Their risky decision-making was measured by the Risky Gains Task.**

Results: **The women with better odour-identification ability made more risky decisions. However, there was no such difference on another cognitive task (Choice RT and Suppress Test), the processing of which involves frontal substrates other than the orbitofrontal region.**

Conclusion: **These findings provide preliminary insight into the phenomenon that performance on tests of prefrontal functions could relate to each other if the functions share similar prefrontal substrates.**

Key words: frontal regions; cognitive rehabilitation; neurorehabilitation; olfaction; risky decision-making.

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INTRODUCTION

Of all of the different cognitive abilities, those subserved by prefrontal regions play a central role in optimal neuropsychological functioning for human survival. Yet, rehabilitating prefrontal functions compromised in brain injuries has always been challenging. In situations when the input/output pathways of the function are impaired, direct training of the compromised ability may not be effective. In those cases, other routes to training must be identified.

Previous literature has suggested the potential of training a specific function via the stimulation of another function, a phenomenon known as cross-modal stimulation. For example, visual stimuli from "mirror therapy" can improve motor function of a poorly functioning arm. Also, in a case study, Sathian and colleagues (1) found that mirror therapy helped a stroke patient regain functionality in an upper limb. In addition, an olfactory-motor cross-modal study by Rossi and colleagues (2) showed that sniffing alimentary odourants increased the motor potentials evoked in hand muscles represented in the motor cortex. In other words, the complex nature of our brain might make it possible to train functions indirectly.

Because the prefrontal regions subserve a high number of processes, many frontal perceptual and cognitive processes share similar neural substrates. For example, olfactory processing is a major frontal perceptual function that depends on the orbitofrontal cortex (OFC; 3, 4). At the same time, the OFC plays an important role in higher cognitive functions, such as risky decision-making (5–7), including decisions about forming new friendships, joining new social groups, financial management, and independent living. Given the nature of the functional neuroanatomical relationships in the frontal regions, it is possible that if two functions are subserved by similar prefrontal substrates, performance on those two functions would be related (8). Hence, it is possible that stimulating one function could affect the performance of another function.

Previous reports have described how performance of different functions subserved by the frontal lobes are related (9–12), such as attention and working memory (13, 14), both of which share similar neural substrates in the dorsolateral prefrontal cortex and the anterior cingulate cortex (15, 16). Westervelt and colleagues (12) found that odour identification was strongly correlated with language ability, and weakly correlated with executive functions. They suggested that the olfaction-language relationship might exist because the two processes share temporo-limbic structures, while the relationship between

olfaction and executive functions might be weak because the two have dissimilar frontal substrates. The olfaction-cognition association has also been reported in some clinical populations, such as: children with attention deficit/hyperactivity disorder (17), people with schizophrenia (18, 19), and elderly people with Alzheimer's disease (20, 21). These studies provide an initial insight into the possibility that different abilities are related because they share similar neural substrates.

The present study examined whether performance was similar on prefrontal perceptual and cognitive processes that shared similar frontal substrates. Specifically, this study tested whether people with high odour-identification ability were also more risk-prone in their decision-making. To examine this proposed relationship, the present study assessed odour identification, which is processed mainly within the frontal lobe, especially the OFC (e.g. 9, 22) and risky decision-making, which also relies heavily on the OFC (5, 6, 23). Albrecht and colleagues (24) confirmed that odour identification and risky decision-making are subserved by OFC subregions that are neuroanatomically close. Along with the physical proximity of the neural regions for odour identification and risky decision-making, previous lesion studies have also reported that the OFC (particularly the posterior region) is critical for both decision-making (25) and odour identification (9, 26).

The findings of this study shed light on the potential use of cross-modal stimulation to rehabilitate prefrontal functions. For example, if olfactory identification and risky decision-making are related, olfactory training may be used to help to encourage patients to be more willing to accept challenges inherent in making new friends and joining new social groups. Doing so will help them establish strong social support networks and hence contribute to their successful social integration and independent living.

If performance on tests of odour identification and risky decision-making are related, one would expect that people with high or low odour-identification ability differ in risky decision-making. To assess odour-identification ability, this study used the Sniffin' Sticks olfactory test (27). The Risky Gains Task (28) and the defined scores of risk taking (SRT) were used to measure risk-taking behaviour in general, as well as after reward/punishment feedback.

This study also examined the specificity of the relationship between odour identification and risky-decision making; specifically, whether people with high odour-identification ability would perform differently from people with low odour-identification ability on cognitive tasks that involve frontal substrates other than the OFC. To measure other cognitive tasks, this study used the supervisory attention process measured by the Choice RT and the Suppress subtests of the Rotman-Baycrest Battery to Investigate Attention (ROBBIA; 29) because it is largely related to activity in the dorsal prefrontal regions (30, 31), not the OFC. Since odour identification and supervisory attention depend on different frontal substrates, there should be no significant difference in performance on supervisory attention between people of high or low odour-identification ability. Finally, this study only included female participants because previous reports have clearly identified a sex-related difference in olfaction (e.g. 32, 33), as well as risky decision-making (e.g. 7, 33).

METHODS

Participants

The participants were 44 healthy, right-handed, Cantonese-speaking, Chinese female participants, age range 23–55 years (mean age 34.59 (standard deviation (SD) 9.36) years). The study was approved by the ethics committee of The University of Hong Kong. Participants were excluded if they currently used medication of any kind or had a history of psychiatric or neurological disorders, head injuries, physical disabilities, or substance use. Informed consent was obtained from each of the participants.

The 44 participants were then further classified into two groups according to their performance on the Sniffin' Sticks odour-identification test (27) (Table I). A mean-split was performed to dichotomize the participants into a high odour-identification ability group (HOI; $n=27$) and a low odour-identification ability group (LOI; $n=17$) according to their odour identification scores (mean 13.05 (SD 1.73)). The mean-split was used for classification of group membership because the Sniffin' Sticks odour-identification test was only an indirect behavioural measurement of odour identification; thus it was unable to provide precise information about individual differences in odour identification.

The HOI group was significantly better at odour identification than the LOI group ($t[42]=7.89$, $p<0.001$). There were no significant differences between the HOI and LOI groups in age ($t[42]=-1.91$, $p>0.05$), years of education ($t[42]=-0.71$, $p>0.05$), or general intellectual ability, as estimated by Raven's Progressive Matrices ($t[42]=1.55$, $p>0.05$; 34).

Materials

Odour-Identification Test. The odour-identification test is a component of Sniffin' Sticks developed by Kobal and colleagues (27). The test consists of 16 pens containing different common odours. In each trial, the participants were presented with 1 of the odour-containing pens 2 cm from their nostrils, and they were required to identify each odour by choosing from a list of 4 descriptors. An odour-identification score was calculated by the total number of correct identifications made from the 16 pens (ranging from 0 to 16).

Risky Gains Task (RGT). In the RGT, participants are presented with 3 numbers (20, 40 and 80) each for 1 s, in ascending order (28). The participants receive the number of points shown on a counter on the screen if they press the designated button on the keyboard. They are further informed that for both 40 and 80 points there is a chance that a –40 or –80 may appear. The negative sign signals those points will be deducted. This setup makes the trials of 40 and 80 risky choices. The probabilities of –40 or –80 appearing are such that the final score would be identical whether the participants consistently selected 20, 40, or 80. Thus, there is no inherent advantage to selecting the risky response (40 or 80) over the safe response (20).

Table I. *Characteristics of the high odour-identification ability group (HOI) and the low odour-identification ability group (LOI) (*n = *44). No significant differences were observed (*p > *0.05)*

Characteristics	HOI Mean (SD)	LOI Mean (SD)
Age, years	31.53 (7.15)	36.52 (10.18)
Years of education	15.24 (1.95)	15.67 (1.94)
Raven's	55.24 (2.91)	53.78 (3.13)
Odour-identification score	14.71 (0.85)	12.00 (1.24)

Raven's: Raven's Progressive Matrices score.

This study calculated risk-taking behaviour and reward-punishment learning with the scores of risk taking (SRT) as follows:

1 Number of risk-taking choices: the sum of the total number of 40 and –40 trials weighted by 1 and the total number of 80 and –80 trials weighted by 2.
2 Total SRT (SRT_{total}): number of risk-taking choices divided by the total number of trials in the task.
3 SRT after safe choice (SRT_{safe}): number of risk-taking choices made immediately after safe-choice trials (i.e. 20) divided by the total number of trials following a safe choice.
4 SRT after risky reward (SRT_{rew}): number of risk-taking choices made immediately after risky reward trials (i.e. 40 or 80) divided by the total number of trials after receiving a risky reward.
5 SRT after punishment (SRT_{pun}): number of risk-taking choices made immediately after penalty trials (–40 or –80) divided by twice the number of trials following a penalty.

Rotman-Baycrest Battery to Investigate Attention (ROBBIA). Two subtests of the ROBBIA (Choice RT and the Suppress Task) were selected to assess the functioning of the Supervisory Attention System (SAS). The Choice RT subtest has 2 conditions. The first condition requires the participants to press the "1" button when the letter "A" is presented. In the second condition, 1 of the 4 stimuli (the letters A, B, C and D) are presented each time, and the participants are required to press "1" for letter "A" and "2" for letters "B", "C" or "D". The effect of choice is defined as the difference between the mean reaction times of the 2 conditions.

In the Suppress subtest, a red or blue letter is presented in each trial. A red "X" and a blue "O" are targets; a blue "X" and a red "O" are distractors; and any other letters are "other stimuli." Participants are required to press "1" for the targets and "2" for both the distractors and other stimuli. Suppression interference is calculated as the difference between the reaction times in responding to the target stimuli and to the distractor stimuli divided by the reaction time in responding to the other stimuli.

Procedure

All of the participants were assessed in a one-on-one session. After completing an intake form that provided their demographic data and medical information, they were tested on Raven's Progressive Matrices. These scores provided estimates of their general intellectual functioning. Each participant took the Sniffin' Sticks test, the computerized RGT, and then the Choice RT and Suppress subtests.

Data analysis

Independent-samples *t*-tests were performed to test for group differences between the LOI and HOI groups in terms of demographics (age, years of education, and performance on Raven's Progressive Matrices), odour-identification scores, SRT_{total}, and indices on the Choice RT and the Suppress subtests. A repeated-measures analysis of variance (ANOVA) was performed to test the effect of each group and different consequence types in the previous trial (safe choice vs risky reward vs risky punishment) on the SRT. One participant was not included in the ANOVA because she did not make any safe choices (in other words, it was impossible to calculate the SRT after a safe choice). Cohen's *d* and partial eta-squared were calculated to show the effect sizes for the *t* tests and ANOVA, respectively.

RESULTS

In the RGT, there were no significant differences in the frequency of taking the safe choice of +20 ($t[42] = -1.88$, $p > 0.05$, $d = 0.57$) or the total frequency of the risky choices of +40 and –40 ($t[42] = 0.35$, $p > 0.05$, $d = 0.11$). The HOI group chose +80 and –80 significantly more frequently than the LOI group ($t[42] = 2.33$, $p = 0.02$, $d = 0.69$).

The participants in the HOI group scored significantly higher than the LOI group on the SRT_{total} ($t[42] = 2.21$, $p = 0.03$, $d = 0.67$), showing that the HOI group had a higher general tendency to take risks. Any differences in risk-taking behaviour between the LOI and HOI groups following different types of outcomes during the task were then investigated. A repeated-measures ANOVA revealed a significant main effect of group ($F[1,41] = 4.62$, $p = 0.04$, $\eta^2_{p=}0.10$). The HOI group generally took more risks than the LOI group. A significant main effect was also found between different consequence types ($F[2,82] = 8.23$, $p < 0.01$, $\eta^2_{p=}0.17$). No significant interaction was found between group and consequence types ($F[2,82] = 1.54$, $p = 0.22$, $\eta^2_{p=}0.04$).

For SAS functioning, the HOI and LOI groups had no significant differences in their performance on the Choice RT and the Suppress subtests. In the Choice RT task, the groups did not have different reaction times on the more demanding choice condition ($t[42] = -0.62$, $p > 0.05$, $d = 0.19$). In the Suppress task, there was no significant difference between the HOI and LOI groups in their suppression interference ($t[42] = 0.04$, $p > 0.05$, $d = 0.01$) (Table II).

Table II. *Group comparison of variables in the Risky Gains Task and the Rotman-Baycrest Battery to Investigate Attention*

	HOI Mean (SD)	LOI Mean (SD)	*t*	df	*p*
Choice RT, ms	183.03 (66.43)	195.94 (67.11)	–0.62	42	0.54
Suppress, ms	134.67 (98.40)	141.74 (119.46)	–0.20	42	0.84
Risky Gains Task					
Frequency of "+20"	20.47 (18.09)	32.48 (22.06)	–1.88	42	0.07
Frequency of "+40" and "–40"	45.53 (11.30)	43.96 (15.39)	0.36	42	0.72
Frequency of "+80" and "–80"	29.94 (14.81)	19.52 (14.00)	2.35	42	0.02*
Total SRT (%)	54.90 (16.30)	43.23 (17.50)	2.21	42	0.03*
SRT after safe choice (%)	47.94 (14.21)	40.42 (20.03)	1.34	41[a]	0.19
SRT after risky reward (%)	57.96 (19.16)	50.44 (18.28)	1.31	42	0.20
SRT after punishment (%)	52.76 (16.61)	37.60 (20.14)	2.59	42	0.01*

*$p < 0.05$; [a]1 participant was not included in the test because she did not make any safe choices throughout the task.
HOI: high odour-identification ability group; LOI: low odour-identification ability group; RT: reaction time; SRT: score of risk taking; SD: standard deviation; df: degrees of freedom.

DISCUSSION

The results of this study indicate that women with better odour-identification ability were more risky in their decision-making. As such, the data are largely consistent with the findings of previous studies (9–16) and supported our first *a priori* hypothesis. The behavioural coupling of performance on tests of odour identification and risky decision-making is an important observation because it gives important insight into the possibility of altering risky decision-making by training of olfactory identification and vice versa. According to the current findings, olfactory training may be used to help regulate risky decision-making in patients who have social anxiety that deters them from attempting social outreach and hence hinders their successful social integration.

Our findings also indicated that participants with high or low odour-identification ability did not differ from each other in supervisory attention. This observation is consistent with the prediction set out in the second *a priori* hypothesis. It also suggests that there is a specific relationship between the 3 variables studied. That is, performance of tasks was related only when they shared the same neural substrates.

Westervelt and colleagues (12) found a less specific olfaction-cognition relationship in older adults. Taking their findings into consideration, and given the fact that the participants in this study were young healthy adults, age may be a significant factor that modulates the relationship between olfaction and cognition, or functions sharing similar/dissimilar neural substrates. This question is certainly worth further study.

During odour identification, when an odour is presented, it is important for the OFC to effectively integrate the physical and emotional factors into a degree of pleasantness (35, 36). This would allow accurate matching of the given pleasantness with the pleasantness of those previously encoded odour objects. Semantic labels of the odour object with similar pleasantness are then retrieved for identification. In other words, better ability in odour identification may reflect effective OFC functioning for the integration of information for odours into a more accurate level of pleasantness for correct identification. During risky-decision making, the valuation process subserved by the OFC is in the least demand when a safe choice is opted for, as there is zero prediction error associated with choosing the safe option. In contrast, taking risky choices could lead to uncertain gains (+40 or +80 points) or losses (–40 or –80). Hence, processing risky rewards would require an appreciation of the factual positive or negative outcome and, at the same time, the generation of a somatic state that includes the respective positive and negative effects. The OFC would then integrate the rewarding factual and somatic information and update the subjective value of different choices (5, 37). According to Prospect Theory (38), decisions are guided by subjective values rather than the objective expected values of choices. Hence, although risky choices can also lead to losses (–40 or –80 points), the effect of the risky rewards could outweigh the effect of punishment when making risky choices. As such, the effective integration of information in the OFC may lead to a higher subjective value of the risky choices when all alternatives are of equal expected value, resulting in a greater readiness to take risks.

From the discussion above, it is clear that the OFC has an important role in integrating information during odour identification (physical pleasantness and somatic state), as well as risky decision-making (factual reward and somatic states). This study found that people with high odour-identification ability are more inclined to take risk than people with low odour-identification ability. Hence, it seems that when a prefrontal substrate serves two processes, the functioning of that prefrontal substrate may be reflected in both processes that it serves, and behavioural performance of these processes is related. This study found that performance on tests of odour identification and readiness to take risks were related. Future connectivity studies on the neural correlates between olfactory identification and risky decision-making may further elucidate the validity of our speculation and decode the nature of the relationship between the two processes. Also, future clinical trials of the effectiveness of cross-modal stimulation in cognitive rehabilitation could test the translational value of the empirical findings of this study.

It is worth noting that our data are unable to determine whether or not the increased risk-taking behaviour associated with better olfactory function is beneficial to the individuals studied. Although previous reports have discussed impulsive risk-taking behaviour in patients with prefrontal damage and drawn a general impression that risk-taking behaviour could be disadvantageous and maladaptive, in this study the calculated risk-taking in our participants may not be maladaptive or disadvantageous. Also, Bechara and colleagues (5) observed that patients with orbitofrontal damage could also be conservative in risk taking while exhibiting a maladaptive pattern of decision-making (39).

Clinical implications

Traditional neurorehabilitation regimes have used direct task-training methods to improve impaired functions. The findings of this study shed light on a new possible neurorehabilitation regime: training a related function may impact the performance of another function subserved by the same neural substrate. This is especially valuable in situations when the input/output pathways of the function are impaired. Rehabilitation may proceed by training another function that shares a similar neural network as the one that was impaired in the disease process.

Limitations

The design of this study is unable to demonstrate a cause-and-effect relationship. Longitudinal experiments could shed more light on cause and effect by examining how the manipulation of performance on one cognitive or perceptual process influences the performance of another process that shares similar prefrontal substrates.

Another limitation is that using mean splits to dichotomize participants into separate groups remains controversial. There are a number of caveats to using dichotomization (40). For instance, dichotomization may result in the loss of statistical

power and effect size, spurious significant effects, or loss of information about individual differences. This is, of course, a limitation of the present study. Future studies can use more sensitive and direct measures of odour identification so that all information about individual differences in odour sensitivity can be confidently included in statistical analyses. This would increase statistical power to reveal any intricate relationship between odour sensitivity and risk-taking behaviour.

Previous studies have demonstrated sex-related differences in decision-making (7, 33) and odour-identification ability, with women identifying odours better than men (31, 41). Hence, the positive relationship between odour identification and risk-taking may not necessarily be the same in men, who generally take more risks but have poorer odour-identification ability. Future research may study sex-related differences that might moderate this kind of olfaction–decision-making relationship.

Conclusion

This study explores the potential of cross-modal stimulation in cognitive rehabilitation by understanding functional relationships of processes subserved by similar prefrontal substrates – the OFC. The findings help delineate the relationship between olfaction and decision-making: Better odour identification was associated with more risk-taking when preceding decisions had led to a loss. This observation serves as a strong starting point for investigating the relationship between prefrontal lobe functions and the application of this understanding for the rehabilitation of prefrontal functional impairment.

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