The Biology and Clinical Relevance of Somatostatin Receptor Scintigraphy in Adrenal Tumor Management

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Somatostatin receptors are present in the normal adrenal cortex and medulla. These receptors are also expressed by tumors that cause Cushing’s syndrome and by pheochromocytomas. Somatostatin analogues such as octreotide have been developed to target somatostatin receptors for diagnostic and therapeutic purposes. This article reviews the current knowledge of the biology of somatostatin receptors in the normal adrenal gland and in adrenal tumors and defines the current role of the somatostatin receptor in the diagnosis, staging and management of Cushing’s syndrome and pheochromocytomas.

INTRODUCTION

The adrenal glands are paired endocrine glands located atop the kidneys. Each adrenal gland has a cortex and a medulla. The adrenal cortex is subdivided into three layers, each with a distinct role in hormone production. The outermost “zona glomerulosa” is the site of aldosterone production, the middle “zona fasciculata” produces cortisol and the innermost “zona reticularis” is the site of adrenal androgen production. The adrenal medulla is part of the neuroendocrine system, receiving sympathetic innervation and producing catecholamines, epinephrine and norepinephrine. Researchers have begun to investigate the importance of the presence of somatostatin hormone receptors on adrenal tissues. The purpose of this article is to review what is currently known about the presence of somatostatin receptors in normal adrenal tissue and adrenal tumors. Next, the use of radiolabeled somatostatin analogues for the diagnosis of adrenal pathology will be discussed. Finally, the potential use of somatostatin analogues for the treatment of adrenal disorders will also be addressed.

NORMAL ADRENAL SOMATOSTATIN RECEPTORS

Somatostatin, also called somatotropin releasing inhibitory hormone (SRIH), is a peptide hormone that is present in two predominant isoforms: a 14 amino acid structure (SRIH-14) and a 28 amino acid form (SRIH-28) [1, 2, 3]. Each of these naturally occurring isoforms binds to all five of the known somatostatin receptors (SSTR1-5) that have been identified in humans [4]. When five normal human adrenals were examined by

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Abbreviations: SRIH, somatotropin releasing inhibitory hormone (somatostatin); SSTR, somatostatin receptor subtype 1-5; 125I, iodine-125; mRNA, messenger ribonucleic acid; cDNA, complementary deoxyribonucleic acid; ACTH, adrenocorticotropic hormone (corticotropin); CRH, corticotropin releasing hormone; MRI, magnetic resonance imaging; IPS, inferior petrosal sinus; SRS, somatostatin receptor scintigraphy; MBq, milli-barq; 111In-DPTA-Phe1-octreotide, indium 111-diethylene triamine penta-acetic acid phenylalanine-1-octreotide; mCi, milli-Curie; 131I-MBG, Iodine 131-meta-iodobenzylguanidine; SPECT, single photon emission computed tomography; CT, computed tomography.
radioautography for specific binding of radiolabeled somatostatin (\(^{125}\text{I}-\text{SRIH}\)), somatostatin receptors were identified in both cortex and medulla, but specific binding was much more intense in the normal human adrenal medulla [5]. In a study of two normal human adrenal glands, messenger ribonucleic acid (mRNA) for each of the five SSTR subtypes was expressed, with SSTR\(_2\) predominating [5]. In summary, the normal human adrenal gland contains all five of the known somatostatin receptor subtypes. The predominant isoform is SSTR\(_2\), and the receptors are concentrated in the adrenal medulla.

Animal studies have been performed in an attempt to gain further insight into the role of somatostatin receptors within the adrenal cortex. In salt-depleted rats, the site of highest somatostatin receptor density in the adrenal cortex is the zona glomerulosa [6, 7]. Administration of somatostatin to these animals specifically inhibits angiotensin II-stimulated aldosterone production. In addition, somatostatin inhibits the basal and angiotensin II-stimulated growth of the rat zona glomerulosa [8]. These animal studies demonstrate that under the given experimental conditions, rat adrenal cortical somatostatin receptors are located mainly in the zona glomerulosa, regulating angiotensin II-mediated aldosterone secretion and growth of the adrenal cortex.

**SOMATOSTATIN RECEPTORS AND ADRENAL DISEASE**

*Pheochromocytomas*

Pheochromocytomas are neuroendocrine tumors arising from the adrenal medulla, which characteristically overs-secrete catecholamines, producing a clinical syndrome of paroxysmal hypertension, heart palpitations and profuse sweating [9, 10]. Paragangliomas are similar tumors, which arise from sympathetic ganglionic tissue and are also known as ectopic or extra-adrenal pheochromocytomas. Approximately 10 percent of pheochromocytomas are malignant. In a study of 51 adrenal pheochromocytomas (46 benign and five malignant), 37 of 51 had SRIH receptors (73 percent) detectable by \(^{125}\text{I}-\text{SRIH}\) radioautography. Only 36 percent of the tumors studied were classified as containing a high density of receptors [11]. However, 13 of 14 paragangliomas studied in the same paper were SRIH receptor positive (93 percent), with 43 percent considered to be of high density.

In a separate study of 33 human pheochromocytomas (22 benign adrenal, six extra-adrenal and five malignant), SSTR was detected in all tumors, but 12/33 pheochromocytomas had a receptor density that was at or below the normal range [5]. In these same tumors, specific binding of radiolabeled somatostatin (\(^{125}\text{I}-\text{SRIH}\)) was found to be evenly distributed over the tumor tissue and was on average significantly increased (two-fold) over normal adrenal medullary tissue. There was no detectable difference in the density of SSTR expression among the subgroups of pheochromocytomas studied. A substudy of SSTR mRNAs quantified by amplification of their respective cDNAs in eight pheochromocytomas (four benign adrenal, two benign extra-adrenal and two malignant), reported in the same paper, revealed that all five SSTR subtypes may be expressed by pheochromocytomas, with multiple subtypes expressed by a single tumor. This confirmed a previous study by a separate group who identified multiple SSTR\(_1\) and SSTR\(_2\) isoforms in each three of the three pheochromocytomas examined [12]. The predominant somatostatin receptor subtypes expressed by pheochromocytomas are SSTR\(_2\) and SSTR\(_4\) [5]. Four out of five malignant tumors had normal or low SSTR expression, and these tumors had a poorer clinical outcome than the single malignant tumor with increased receptor density.

In summary, the majority of pheochromocytomas express somatostatin receptors at similar or increased density compared to normal adrenal medullary tissue. Receptor subtype expression and density vary case-to-case.
Adrenal cortical tumors

No systematic study of somatostatin receptors in adrenal cortical tumors has been published to date. Despite this dearth of scientific information, clinicians have attempted to target somatostatin receptors on those clinically challenging tumors which overproduce cortisol and are located outside the adrenal gland. The results of these clinical efforts at diagnosis and therapy are discussed below.

SOMATOSTATIN RECEPTOR SCINTIGRAPHY

Octreotide is a man-made eight amino acid analogue of the 14 amino acid naturally occurring hormone somatostatin. Octreotide has an elimination half-life of two hours, much longer than the three-minute circulation half-life of somatostatin, and is thus better suited for use in the diagnosis of somatostatin receptor positive tumors [3, 13]. 111In-pentetreotide (OctreoScan®, Mallinckrodt Medical Inc., St. Louis, Missouri) is currently available as a diagnostic agent in the United States. Its use in the management of tumors affecting the adrenal gland is summarized below.

ACTH-dependent Cushing’s syndrome

Octreotide scanning has proven helpful in the diagnosis of selected cases of extra-adrenal tumors producing adrenocorticotropic hormone (corticotropin or ACTH) or corticotropin releasing hormone (CRH). Excess secretion of these hormones results in an overproduction of cortisol from the adrenal gland, a condition called ACTH-dependent Cushing’s syndrome. Patients present with hypertension, central obesity, diabetes, easy bruising, rounded facies, plethora, hyperpigmentation and purple abdominal striae. ACTH-dependent Cushing’s Syndrome may stem from either a primary pituitary tumor (Cushing’s disease) or from an ectopic source. The most common ectopic tumor is a carcinoid tumor located in the chest or gut. Somatostatin receptor scintigraphy has proven most beneficial for diagnosing occult ectopic tumors.

Patients are diagnosed with ACTH-dependent Cushing’s Syndrome based upon elevated serum or urine cortisol measurements, with simultaneous elevation of ACTH [14]. Further biochemical suppression tests are then performed in an attempt to differentiate the source of the abnormal hormone production either to the pituitary or periphery [14, 15]. When these studies are non-diagnostic, the pituitary may be visualized with magnetic resonance imaging (MRI) to attempt to identify obvious disease. In equivocal cases, inferior petrosal sinus (IPS) sampling for ACTH with and without CRH stimulation is performed to document whether the excess hormone production is of a central pituitary or peripheral ectopic source [16]. It is in those cases isolated to the periphery that somatostatin receptor scintigraphy has been of most diagnostic benefit.

Initial evidence for the potential benefit of SRS was tested in a study of 10 patients with ectopic Cushing’s syndrome (nine ectopic ACTH-secreting tumors and one CRH-secreting tumor) with a total of 24 known localizations and one occult tumor. In five of the 10 patients, SRS identified all known localizations, and in eight of 10, identified at least one known site. Nineteen of the 24 known localizations were correctly identified (79 percent) [17, 18]. The one occult tumor remained occult despite the octreotide scan. No information about possible false-positive localizations was included in the report. Thus, this report suggested that in up to 79 percent of lesions may be identified by SRS in cases of ectopic Cushing’s, localizing all sites in 50 percent of subjects. In this same study, nine other patients with pituitary or adrenal sources for their excess hormone production (five pituitary Cushing’s disease, three Nelson’s syndrome and one adrenal adenoma) had negative scans, suggesting these tumors do not overexpress somatostatin receptors.
Actual tumor size is of little importance in octreotide scanning. It is the increased density of somatostatin receptors expressed by the tumors compared with neighboring tissues that allows the tumor to be visualized [19]. For this reason, tiny producing tumors that overexpress somatostatin receptors may be easily visualized with octreotide scanning. Three additional case reports have been published in which SRS localized minute carcinoid tumors (1.0 cm, 0.9 cm and 0.6 cm) that were responsible for ACTH-dependent Cushing’s syndrome in patients. [20, 21, 22]. SRS identification (two patients) and confirmation (one patient) of these small lesions was clinically important as their signal characteristics were difficult to distinguish from pulmonary blood vessels by conventional imaging, and surgical removal of these lesions leads to prompt cure.

SRS and pheochromocytoma

Despite the extensive in vitro data that has been published regarding the presence of somatostatin receptors on pheochromocytomas, the published clinical experience with somatostatin analogues such as radiolabeled octreotide to image pheochromocytomas in vivo has been limited to two small European case series. In the largest series published to date, 12 out of 14 pathologically confirmed pheochromocytomas (86 percent) were identified by $^{111}$In-DPTA-PhEG-Octreotide (222 MBq intravenous with planar imaging four hours post-injection and planar plus SPECT imaging at 24 hours) [23]. This same group reported a diagnostic sensitivity of 93 percent for the localization of paragangliomas (26 out of 28) using the same protocol [23, 24]. No information regarding false positive localizations was stated.

Our own preliminary experience with SRS and pheochromocytomas involves an ongoing comparison of SRS with standard imaging modalities (CT or MRI) at the Brigham and Women’s Hospital in Boston [25]. Patients with a high clinical suspicion of pheochromocytoma based upon biochemical testing and the presence of a CT or MRI documented lesion underwent SRS (6.0 mCi $^{111}$In-pentetreotide with planar imaging at four and 24 hours and SPECT imaging at 24 hours). All suspicious lesions were then evaluated at surgery and identified with pathology. SRS accurately localized five of six pheochromocytomas. Two benign lesions felt to be suspicious for pheochromocytoma based on MRI were appropriately negative on SRS. Thus, this small series demonstrates that SRS has a sensitivity of 83 percent for pheochromocytoma (five of six lesions), comparable to the European experience. In our experience, SRS localizes adrenal, ectopic and metastatic pheochromocytomas. Prospective multi-center studies are needed in order to obtain the necessary numbers of patients to more firmly establish the sensitivity and specificity of this test.

The other published study addresses the important clinical consideration of the relative sensitivity of SRS compared to the current gold standard nuclear medicine compound utilized in the evaluation of pheochromocytoma, MIBG [26]. The sensitivity of MIBG scanning for pheochromocytoma has been well established, based in part on a prospective study of 109 patients with a high clinical suspicion for pheochromocytoma who received extensive biochemical testing, CT scanning and a diagnostic $^{131}$I-MIBG (45 surgically confirmed cases of pheochromocytoma, 20 non-pheochromocytoma adrenal masses and 44 considered clinically free of disease based on the diagnostic workup) [9]. MIBG had a sensitivity of 78 percent (35 out of 45 confirmed pheochromocytomas imaged), a specificity of 100 percent (0 out of 20 adrenal adenomas imaged), yielding a negative predictive value of 87 percent and a positive predictive value of 100 percent in this series.

SRS using $^{111}$In-DPTA-PhEG-Octreotide (130-187 MBq intravenous with planar imaging at four, 24 and 48 hours and SPECT imaging at 24 hours) was compared with MIBG scanning in 10 patients with metastatic pheochromocytomas and three patients with paragangliomas [26]. The type and dose of MIBG varied widely among the study
subjects. Among the 10 pheochromocytoma subjects, six received a diagnostic dose of MIBG (five received 74 MBq 123I-MIBG, one received 370 MBq 131I-MIBG) and four received a therapeutic dose of MIBG [3.7 GBq 131I-MIBG]). Scans were evaluated by blinded investigators, and sites were confirmed by histologic examination of surgical specimens for chromaffin tissue when available. SRS identified at least one lesion in nine of 10 subjects with pheochromocytoma while MIBG identified tumor in eight of 10. MIBG, however, localized over 80 lesions in these patients, while octreotide only identified 28. Soft tissue lesions were identified equally well with both techniques, although in general, the intensity of uptake was greater for MIBG. MIBG was superior, though, for the localization of bone metastases [26]. Overall, octreotide identified only 43 percent of sites seen by the diagnostic MIBG scans, and only 24 percent of the sites identified on therapeutic MIBG. Octreotide scanning fared far better in the three subjects with paragangliomas identifying at least one site in all three patients and eight sites overall, compared to the nine sites seen by MIBG in the three subjects.

There was one pathologically confirmed lung metastasis that was missed by MIBG but identified by octreotide. However, the abdominal primary in this same patient was missed by octreotide but seen on MIBG. This raises the possibility that octreotide scanning may be complementary to MIBG scintigraphy. This concept was tested further by Krenning and colleagues in an analysis of eight patients with pheochromocytoma and four subjects with paraganglioma. Two patients with pheochromocytoma who received both scans had more lesions seen with octreotide, while two had more lesions seen with MIBG. Four patients had the same number of lesions visualized. Three out of four patients with paragangliomas had more sites identified with octreotide than MIBG [23]. Therefore, the sensitivity of these nuclear imaging techniques appears to depend on type of tumor and suspected location of metastases. MIBG appears more sensitive for pheochromocytoma metastases to bone, while octreotide may be preferred for pheochromocytoma metastases to lung and for cervical paragangliomas [23, 26]. Future studies comparing SRS to MIBG utilizing a consistent amount of nucleotide in each subject are needed to more accurately assess the relative sensitivities of these techniques as dosimetry affects the diagnostic sensitivity of radionuclide imaging.

**Clinical algorithms for SRS in Cushing’s syndrome and pheochromocytoma**

A critical question for the clinician is the appropriate use of radionuclide imaging in the management of a patient with either a suspected or pathologically confirmed case of Cushing’s or pheochromocytoma. Until further prospective studies are completed, which would establish the sensitivity, specificity and cost effectiveness of SRS, clinical judgment will dictate its use on a case-by-case basis [27].

The diagnosis of ACTH-dependent Cushing’s syndrome should be established biochemically prior to any imaging being performed (Figure 1). Next, a dexamethasone suppression test and a pituitary MRI is performed to localize the lesion. A diagnostic suppression test in conjunction with a localization by pituitary MRI is followed directly by surgical resection of the identified lesion. Negative pituitary MRI in conjunction with non-diagnostic suppression or markedly elevated ACTH levels strongly suggests a peripheral source and should be initially followed by SRS and chest and abdominal CT scans to localize the tumor. A positive localization will avoid the invasive IPS procedure in these patients. Other cases in which the dexamethasone suppression test and pituitary MRI provide conflicting data require IPS sampling for ACTH to confirm if the lesion is central or peripheral. If the IPS sampling suggests a peripheral source, SRS and CT scanning should now be performed to localize the tumor. When the source cannot be localized by any technique, medical management or bilateral adrenalectomy is considered. All localized tumors
Figure 1. Octreotide scan in the differential diagnosis of ACTH-dependent Cushing’s syndrome. a) 2 mg dexamethasone by mouth every six hours for 48 hours; b) MRI: magnetic resonance imaging; c) Suppressed: >90 percent suppression of urine free cortisol or >64 percent suppression of 17-hydroxycorticosteroids from baseline urine [16]; d) IPS: inferior petrosal sinus sampling for ACTH; e) SRS: somatostatin receptor scintigraphy with $^{111}$In-pentetreotide; f) CT: Computed tomography. g) Positive Sampling: peak IPS: peripheral ratio of ACTH greater than 3.0 with CRH administration [16].

are resected. Pheochromocytomas and paragangliomas should first be diagnosed biochemically and then localized with MRI (Figure 2). If a benign appearing adrenal mass is identified, the patient may proceed directly to surgical resection. If no mass is seen, an octreotide scan or MIBG scan is performed to localize the source. Choice of scan depends upon availability and local expertise. A positive scan avoids the need for invasive venous sampling. In adults, 10 percent of pheochromocytomas may be ectopic, 10 percent malignant and 10 percent bilateral [10]. Extra-adrenal and malignant lesions identified by MRI should be confirmed with nuclear imaging to document the neuroendocrine nature of the lesions and to rule out extra-abdominal metastases. Patients with persistent post-resection hypertension and catecholamine excess would also benefit from a follow-up nuclear scan to rule out recurrent or residual disease that may be obscured by post-operative changes on MRI.
Figure 2. The role of somatostatin receptor imaging in the staging of pheochromocytoma. a) MRI: magnetic resonance imaging; b) SRS: somatostatin receptor scintigraphy; c) MIBG: meta-iodobenzylguanidine; d) Venous sampling: venous catheterization with sampling for catecholamines along the superior and inferior vena cava [20].

**CURRENT SENSITIVITY AND SPECIFICITY OF SRS**

Several caveats must be kept in mind when using somatostatin receptor scintigraphy for the identification of adrenal tumors. There has been no study published to date that adequately addresses the specificity of SRS. It is known, however, that activated lymphocytes overexpress somatostatin receptors. Positive octreotide scans, therefore, occur in sites of granulomatous disease (23 of 23 cases of sarcoid, four of four cases of Wegener’s, and six of six cases of tuberculosis) and in cases of autoimmune inflammation (nine of nine cases of untreated Graves’ hyperthyroidism) [23]. Localized sites of abscess or infection or active sites of rheumatoid arthritis will also result in a positive scan. Up to 75 percent of benign, non-functioning pituitary adenomas may overexpress somatostatin receptors (12 of 16) [23].

The current clinical case series published to date suggest a diagnostic sensitivity of up to 86 percent for benign pheochromocytomas but as low as 24 percent for pheochromocytoma metastases [23, 26]. False-negative scans occur in tumors that do not express receptors. Only 38 of 52 pheochromocytomas (73 percent) examined in one study were SSTR positive in vitro [11]. False-negative scans may also occur if tumor somatostatin
receptors are down-regulated by endogenous somatostatin production. In one study, 23 of 41 pheochromocytomas tested SRII positive (56 percent) with three of three of these positive for SRII mRNA, confirming local production of the hormone [11]. Prior exogenous administration of a somatostatin analogue may also down-regulate receptor expression by tumor. False-negative scans may occur because indium-labeled octreotide is cleared by the kidneys, making imaging of the nearby adrenal glands difficult [23]. Finally, tumors that express a different subtype of somatostatin receptor that the octreotide does not recognize will also be missed by this imaging technique [13, 23]. Octreotide recognizes SSTR2, SSTR3 and SSTR5. Pheochromocytomas rarely overexpress SSTR3 or SSTR5 [5]. Therefore, imaging is dependent chiefly upon the pheochromocytoma overexpressing SSTR2. In a series of eight pheochromocytomas, SSTR2 and SSTR4 were the most abundantly expressed, but SSTR3 only accounted for 40 percent of the overall SSTR expression by these tumors [5]. The development of new somatostatin analogues with different receptor subtype specificities will be critical to enhancing the sensitivity of SRS for the imaging of pheochromocytomas.

**TARGETING SOMATOSTATIN RECEPTORS FOR TREATMENT**

Targeting somatostatin receptors in patients with tumors producing Cushing’s syndrome has met with limited success. Single dose treatment of nine patients with ACTH dependent Cushing’s syndrome with either 

somatostatin (five patients, 500 micrograms intravenous infusion over 60 minutes) or octreotide (four patients, 100 micrograms subcutaneous injection) did not lead to a clinically or statistically significant change in plasma ACTH levels in any patient. In the same study, five other patients with pituitary Cushing’s disease did not have a change in ACTH or cortisol response to 1 microgram per kilogram body weight CRH intravenous after a single treatment with octreotide [28]. In a separate case report, two patients treated with octreotide (100-150 micrograms subcutaneously every eight hours for five to seven days) had no clinically significant decrease in 24-hour urine free cortisol, serum cortisol or ACTH levels [29]. Thus, short-term therapy of unselected cases of Cushing’s with somatostatin analogues is ineffective. Targeting those tumors that overexpress somatostatin receptors based on a positive localization with SRS may prove more effective in specific cases.

Sustained therapy for one month with sandostatin, a long-acting somatostatin analogue (400-1200 micrograms daily intravenous or divided subcutaneously every eight hours for 24-49 days), has proven effective in its ability to decrease the serum ACTH levels of three out of three patients with pituitary Cushing’s disease requiring medical therapy [30]. Another patient with paraneoplastic cortisol hypersecretion reported in the same paper was noted to have a significant decrease in serum ACTH levels as well as a sustained decline in urine free cortisol excretion. The literature also contains a single report of a patient who received symptomatic relief from sustained therapy with a somatostatin analogue for a hormonally active, metastatic, adrenal cortical carcinoma that was resistant to standard chemotherapy [31]. Thus, sustained medical therapy with parenteral somatostatin analogues may be considered as an option to provide symptomatic relief to patients with adrenal cortical stimulating tumors who are non-operative candidates. Risks and benefits of this therapy should be balanced with the risks and benefits of more established medical therapies [14].

Clinical experience with octreotide as a therapeutic agent for pheochromocytoma has not met with success to date. Ten patients with pheochromocytoma in a crossover, placebo-controlled trial were given either three doses of 100 micrograms of octreotide or placebo subcutaneously over 24 hours. Blood pressure and serum and urine catecholamines
were monitored pre- and post-dosing. No change in blood pressure or plasma and urine catecholamines were noted overall. Two of the patients with the highest density of somatostatin receptors on their tumors were noted to have a modest decrease in norepinephrine levels, but this did not translate into a lower blood pressure [32]. Other investigators have shown a fall in norepinephrine and epinephrine levels in six patients treated with 50 micrograms of intravenous octreotide infused over two hours, but without a consistent effect on blood pressure [33].

**FUTURE DIRECTIONS**

A promising area for the therapeutic use of octreotide in adrenal tumor management is to deliver a toxic dose of a radioactive substance directly to tumor cells. Similar technology has been used with $^{131}$I-MIBG, but most tumors respond incompletely and become rapidly resistant to this particular therapy [26, 10]. Radiolabeled somatostatin analogues designed for therapeutic purposes are currently undergoing clinical trials [13].

**CONCLUSION**

In summary, somatostatin receptors are present on both normal adrenal cortex and on tumors producing an excess of adrenal cortical hormones. Imaging of primary adrenal cortical lesions is limited by renal clearance of octreotide and a low somatostatin receptor density. Ectopic or metastatic lesions may be visualized and may partially respond to sustained exogenous treatment with somatostatin analogues. Non-adrenal carcinoid tumors secreting hormones, which stimulate the adrenal gland to overproduce cortisol, are able to be visualized by octreotide. Early use of octreotide scanning may help avoid invasive diagnostic and surgical procedures in patients whose tumors express somatostatin receptors.

The majority of pheochromocytomas and paragangliomas express a high density of somatostatin receptors, and many may be visualized with currently available radiolabeled somatostatin analogues. Further investigation is needed to establish its sensitivity and specificity compared with existing technologies, but clinical use may be considered in patients with documented catecholamine excess and negative or equivocal localization studies.

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